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OF THE

CHEMICAL LABORATORY

OF THE

AMERICAN MEDICAL ASSOCIATION

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LABORATORY STAFF

W. A. PUCKNER, PHAR. D., DIRECTOR

Secretary, Council on Pharmacy and Chemistry, A. M. A.

P. N. LEECH, PH. D.

L. E. WARREN, PH. C., B. S.

PART I. . . . . REPRINT OF CONTRIBUTIONS

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PRESS OF

AMERICAN MEDICAL ASSOCIATION

FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET

CHICAGO

PREFACE

The Chemical Laboratory of the American Medical Association was established in 1906 to assist the Council on Pharmacy and Chemistry of the American Medical Association in the investigation of proprietary and unofficial non-proprietary medicinal preparations offered to the medical profession.

In accordance with the object of its foundation, the A. M. A. Chemical Laboratory concerns itself primarily with the examination of those proprietary and unofficial medicinal preparations which the Council has under consideration. The Laboratory determines if the claims made for the composition of these preparations are truthful, and, when a product is admitted to the Council's publication "New and Nonofficial Remedies," looks after the establishment of standards whereby the identity and purity of such a product may be determined.

In addition to the investigations made for the Council on Pharmacy and Chemistry, the Laboratory aids The Journal of the American Medical Association in supplying the medical profession and the public with information about the character and composition of drugs. This includes the analyses of proprietary medicinal preparations which are offered to the medical profession and which are not deemed worthy of investigation by the Council on Pharmacy and Chemistry, and the analyses of nostrums ("patent medicines") exploited to the public. Through the columns of The Journal and through direct correspondence the Laboratory responds to requests of physicians for information regarding proprietary preparations advertised to physicians and quack nostrums sold to the public, which have come to their notice. A knowledge of the composition of nostrums, whether offered to the medical profession or to the lay public, is generally a sufficient demonstration that many of the therapeutic claims made for such preparations are unwarranted. For this reason the Laboratory strives earnestly to answer all such inquiries, either by reference to avail-

able information or by actual analysis, when it is believed that the results of such investigation will prove of general interest to the medical profession or to the public.

This volume of the Reports of the A. M. A. Chemical Laboratory contains those portions of the Laboratory's activities during 1922 which were believed to be of interest to workers concerned with the examination and standardization of medicines, and includes: (1) reprints of contributions from the Chemical Laboratory of the American Medical Association, (2) reports abstracted from The Journal of the American Medical Association and (3) reports not previously published. Continuing the practice adopted at the foundation of the Laboratory, each report in this volume contains a detailed statement of the analytical methods employed and the results obtained, whenever it was believed that such statement would prove helpful to others engaged in the examination of medicines.

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PART I

REPRINTS OF CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF THE AMERICAN MEDICAL ASSOCIATION

THE DETERMINATION OF DIGITOXIN IN DIGITAN

(Reprinted from the Journal of the American Pharmaceutical Association, January, 1922, p. 8)

L. E. Warren, Ph.C., B.S.

Because of the great value of digitalis in medicine, the chemistry of the drug is a subject of much interest. Although many chemists have devoted their energies to the solution of the problems of digitalis chemistry, the subject, because of its great complexity, still remains only partially solved. A number of proximate principles are reported to have been obtained from digitalis, chief among which are digitoxin, digitalein, digitophyllin, digitonin and gitalin. Since the chemistry of digitalis is in a controversial state, some of these so-called active principles may be shown later to be mixtures or derivatives of more complex substances, originally present in the drug. Alkaloids are not present.

It is generally conceded that the activity of digitalis leaves is due almost entirely to the presence of the glucosides. The physiologic activity of the individual glucosides varies considerably, some being very toxic while others are much less active. The ease with which the glucosides are absorbed by the organism is also an important factor in judging the activity. It seems to be established that the quantities and the proportions in which the individual glucosides exist in digitalis leaves are not constant. This may account for the variable quality of the drug. There has been much controversy as to which of the principles in digitalis is the active therapeutic agent or the chief active therapeutic agent. At one time digitoxin was supposed to have this distinction, but it is now admitted that digitoxin is not the only valuable constituent. At least there are active principles in digitalis other than digitoxin, which have a modifying, additive or synergistic action on the digitoxin.

The chemical assay of digitalis has often been attempted but to date no method satisfactory in all particulars has been evolved. Nearly all of the assay processes proposed endeavor to isolate the digitoxin and either weigh it as such or estimate it by colorimetric methods. One of the earlier methods proposed was that of Keller.[1] Essentially this is as follows:

> The ground leaves (10 gm.) are percolated with 70 per cent. alcohol, the solvent removed by evaporation, the residue taken up in water, an excess of lead acetate solution added, the precipitate removed by filtration, the excess of lead in the filtrate precipitated by sodium sulphate, the lead sulphate removed by filtration, the filtrate made alkaline with ammonia water and shaken successively with small portions of chloroform. The solvent is removed by evaporation, the residue taken up in a mixture of chloroform and ether (3 + 7) and the mixture poured with stirring into an excess of petroleum benzin. The flaky precipitate is collected, washed, dried and weighed.

The Keller assay method was modified by Fromme[2] who used maceration instead of percolation for extracting the drug and employed aliquot parts in place of the clarified entire extract for the completion of the assay. Fromme determined the digitoxin content of a great many specimens of digitalis at this time and in succeeding years. He and Focke[3] questioned whether the digitoxin assay is a reliable index of the toxicity of digitalis, and they concluded that the digitoxin content and the physiological activity of the drug, as determined on frogs, did not run parallel.

Arnold and Wood[4] appear to have been the first to question whether digitoxin represents the total of the therapeutic activity of digitalis. They determined that the average amount of digitalis to kill a given weight (1 kilo) of dog was 0.150 gm. Under the same conditions it required about 0.003 gm. of pure digitoxin to kill. The authors calculated that, since digitalis may be assumed to contain about 0.2 per cent. of digitoxin, the fatal dose of the drug for the dog would contain but 0.0003 gm. of digitoxin or about one-tenth of the amount actually required. In a later report Wood[5] states that, in general, clinical reports indicate that digitoxin has about 25 per cent. of the therapeutic effect of the digitalis from which it is prepared. Any assay of digitalis,

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1. Ber. d. pharm. Ges. **7**: 125, 1897.
2. Caesar and Loretz: Geschäfts-Bericht, 1897, p. 25.
3. Deutsch. Aerzt. Ztg. **6**: 292, 1904; Bull. Hyg. Lab., U. S. P. H. S. **48**: 9, 1909.
4. Am. J. M. Sc. **120**: 165, 1900.
5. Am. J. Pharm. **80**: 107, 1908.

therefore, which is based on digitoxin content discards about three-fourths of the active substance of the drug.

Three specimens of fluid extract of digitalis which had been assayed by the physiological method on frogs, were subjected to the Keller assay by Famulener and Lyons.[6] The results from the few tests made, appeared to show that the method does not give very close duplicates and that the results probably do not indicate correctly the relative strength of the samples assayed.

Ziegenbein[7] investigated the reliability of the Keller-Fromme assay. Using frogs for the tests he compared the activity of digitoxin which had been obtained by the Keller-Fromme method from a given weight of dried digitalis leaves with the toxicity of the extract from the same quantity of leaves. He found the activity of the separated digitoxin to be only from 15 to 40 per cent. of that of the extract. He concludes that the quantity of digitoxin as determined by the assay bears no relation whatever to the toxicity of the drug.

The investigations of Barger and Shaw[8] also showed that the Keller assay is not an index of the strength of galenical digitalis. They assayed commercial specimens of tincture of digitalis by the Keller process, slightly modified, and tested the same preparations by physiological tests on frogs. The separated digitoxin had only about one-half of the toxicity to frogs which was possessed by an equivalent quantity of the original tincture. They prepared an artificial tincture by percolating hay with alcohol and adding a definite weight of digitoxin to it. This tincture was assayed by the Keller method and the resultant substance supposed to be digitoxin was tested on frogs. The activity of this material was only about two-thirds of that expected from the digitoxin taken. The authors concluded that as yet there is no satisfactory method for digitalis assay except the physiological one.

Reed and Vanderkleed[9] assayed nine specimens of digitalis preparations by the Keller method and tested the activity of the same preparations on guinea-pigs. They did not determine the activity of the separated digitoxin. They reported a considerable degree of relationship between the findings by the two methods but, as Edmunds and Hale[10] have pointed out, there are serious exceptions to a perfect parallelism.

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6. Proc. Am. Pharm. A.: **50:** 415, 1902.
7. Arch. Pharm. **240:** 454, 1902.
8. Pharm. J. **73:** 249, 1904.
9. Am. J. Pharm. **80:** 110, 1908.
10. Bull. Hyg. Lab., U. S. P. H. S. **48:** 9, 1909.

Further evidence of the worthlessness of the Keller method has been offered by Tschirch and Walter[11] and by Schmidt and Heyl.[12] Tschirch and Walter tried many methods for the chemical assay of digitalis. The method which they recommended as the best is as follows:

> The leaves are first exhausted with ether by which chlorophyll, fat and resin are removed. They are then treated according to Keller's method but after precipitating with lead acetate, the glucosides are shaken out with acetone, the acetone solution being made to separate by adding sodium chlorid. The solvent is drawn off, evaporated on the water-bath and the residue dried and weighed.

By this procedure it is claimed that a mixture of all the active constituents of the leaves is obtained. The physiological activity of this mixture is, however, less than that of the corresponding quantity of the solution before removal of the active principles, although the residue left after the extraction is quite inactive. Nevertheless, the authors claim that the acetone method is a reliable chemical method of assay, inasmuch as by it all of the active constituents, and not the digitoxin alone, are separated and weighed. The work of Tschirch and Walter, apparently, has not been repeated by other workers so that their method is still in the experimental stage.

It will be seen from this brief review that the Keller assay process, with some modifications, is still considered the best method for the chemical assay of digitalis, unless Tschirch and Walter's method be accepted. However, it has been practically demonstrated that digitoxin does not represent the entire therapeutic virtues of digitalis and that the digitoxin content (as obtained by the Keller-Fromme process) does not run parallel with the therapeutic activity of the drug. Consequently a chemical assay of digitalis for its digitoxin content is of little value in evaluating the drug. Most writers believe that the biologic assay is the only criterion by which proper valuation of the drug may be judged. A few like Reed and Vanderkleed[13] maintain that the Keller method, if carefully carried out, is a valuable adjunct to the biologic assay.

Digitan is a digitalis preparation which is claimed to be a mixture of digitalis glucosides in the form of tannates diluted with milk sugar. Weight for weight it is said to be equivalent to digitalis leaves of standard quality. Digitan was originally called *digipuratum* and was introduced into

11. Schweiz. Apoth. Ztg. **56**: 469, 495, 512, 1918.
12. Am. J. Pharm. **91**: 425, 1919.
13. Ibid. **80**: 110, 1908.

"New and Nonofficial Remedies" under that name. The product is stated to be controlled by the Gottlieb biological method and is standardized so that 0.001 gm. of the substance will permanently stop the heart of a 30 gm. frog within an hour in the majority of cases. The method given in "New and Nonofficial Remedies" (1921) for the chemical assay of digitan (digipuratum) is an adaptation of a part of the Keller process. It omits clarification of the extractives by lead acetate solution. This method was furnished by Knoll and Company at the time the product (digipuratum) was being considered by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in "New and Nonofficial Remedies." No control assays were carried out by the A. M. A. Chemical Laboratory at the time.

Through a series of biologic tests on extractives obtained from digitan by the "N. N. R." chemical assay method, it seemed doubtful whether the method of chemical assay furnished by Knoll and Company was reliable. This would be expected in view of the generally accepted belief in the unreliability of the Keller-Fromme method. However, since the method given by Knoll and Company is a very marked deviation from the Keller-Fromme process and the product is distinctly different from digitalis, it seemed worth while to investigate the subject further. Accordingly, specimens of digitan were purchased and, after thorough mixing, were assayed for digitoxin by the method described in "New and Nonofficial Remedies" in the Laboratory of the American Medical Association. The assays were carried out in duplicate. The method used is as follows:

> Ten gm. of digitan are dissolved with moderate heat in 50 c.c. of water, 5 c.c. of 10 per cent. ammonia water are added and the liquid extracted with chloroform. The chloroformic extractions are filtered into a tared vessel and the chloroform removed by distillation. The residue is dissolved in 3 gm. of chloroform, the solution mixed with 7 gm. of ether and 50 gm. of petroleum benzin and the mixture allowed to stand overnight. The separated flakes are collected on a small filter, the residue on the filter dissolved in absolute alcohol, allowing the solution to run into the tared distilling vessel. The solvent is distilled off and the residue dried to constant weight. The digitoxin thus found should not amount to more than 0.04 gm.

It will be observed that this method limits the digitoxin obtainable from digitan to 0.4 per cent. It should also be noted, as previously mentioned, that the method omits the clarification with lead acetate which is a part of the Keller method.

It had been found in earlier experiments with the assay of digitan that coloring matter (and perhaps other sub-

stances) could be obtained apparently almost indefinitely by repeated shaking with chloroform. In these assays, the alkaline solution of digitan was shaken eight consecutive times with 15 c.c. each of chloroform. This was adopted arbitrarily in lieu of any definite directions concerning the manner in which the shaking is to be carried out and is in agreement with the observations of Tschirch and Walter[14] who found eight shakings to be necessary. In the method originally presented to the Council by Knoll and Company, the directions were to continue the extraction until a portion of the chloroformic extract, after evaporation of the solvent and solution of the residue in glacial acetic acid, would no longer give a greenish blue tint with sulphuric acid containing a trace of ferric iron. This portion of the directions had been omitted from "N. N. R." In the assay, as a matter of record, the chloroformic extracts before purification were evaporated on a gently simmering steam bath, the residues dried over sulphuric acid and weighed. The chloroform-ether-petroleum-ether solutions, from which the substance supposed to be digitoxin had been precipitated, were evaporated to dryness, the residue dried over sulphuric acid and weighed. These fractions were tested for activity by the biologic method.[15] After extraction by chloroform, the alkaline solution of digitan remaining was submitted to biologic tests (after removal of the dissolved chloroform by gentle evaporation). The fraction supposed to be digitoxin was also tested for activity by the pharmacologic method.

Duplicate assays of the specimens of digitan gave, respectively, 1.104 and 1.064 per cent. of substance supposed to be digitoxin, or more than 2½ times the quantity permitted by the standards established by the test.

The results of the chemical examination are tabulated herewith.

Chemical Assay of Digitan

Sample	Weight of Sample	Chloroform Soluble Residue	Chloroform-Ether- Petroleum-Ether Residue	Digitoxin
A	10.0098 gm.	0.1837	0.0682	0.1104
B	10.0037 gm.	0.1822	0.0678	0.1064

14. Schweiz. Apoth. Ztg. **56:** 469, 1918.

15. The several fractions obtained in the digitan assay were tested pharmacologically by Dr. Robert A. Hatcher in the pharmacologic laboratory of Cornell University Medical College. The writer gratefully acknowledges his indebtedness to Dr. Hatcher for the aid rendered and also for many helpful suggestions given.

The digitoxin residue was dissolved in dilute alcohol and the solution diluted with normal salt solution before testing its activity on cats. The toxicity when injected continuously into cats by the intravenous method was found to average 1.8 mg. × kg. of body weight. (Full details of the method and protocols of the findings will be published in the *A. M. A. Therapeutic Research Reports.*) A dose of this residue of 1.5 mg. × kg. of body weight was then injected intravenously into each of three cats, the animals were returned to their cages, after which an interval of three hours was permitted to elapse and the animals were then injected with ouabain solution 1–200,000 until death occurred. The quantity of ouabain required to produce death indicated a toxicity for the residue being tested, of about one-sixth of that of pure digitoxin.

By the same method, the chloroform-insoluble fraction of digitan was found to contain about two-thirds to three-fourths of the total toxicity of the product.

The residue obtained by the evaporation of the chloroform-ether-petroleum-benzin solution from which the digitoxin was supposed to have been precipitated was totally inert.

It is evident that the substance obtained from digitan in the digitoxin assay method as described in "New and Non-official Remedies" is not pure digitoxin. For the determination of digitoxin the method is, therefore, valueless.

ACETYLSALICYLIC ACID IN SODIUM CITRATE SOLUTION

(Reprinted from The Journal A. M. A., Jan. 28, 1922, p. 275)

Paul Nicholas Leech, Ph.D.

Acetylsalicylic acid ("aspirin") is dispensed in dry condition because it is easily decomposed in the presence of moisture; also it is insoluble in water. However, articles have appeared recently in both medical and pharmaceutic literature claiming that acetylsalicylic acid may be dispensed *in solution* by aid of sodium citrate; also that the acetylsalicylic acid would not be decomposed. For instance, the following, which was probably abstracted from some American pharmaceutic publication, appeared in the *Prescriber*:[1]

1. Solvent for Acetylsalicylic Acid. The Prescriber, June, 1921, p. 247.

Acetylsalicylic acid (aspirin) is practically insoluble in water, and though soluble in alcohol such a solution is not generally suitable for administration. It is therefore usually given in tablets or cachets. Solution may be effected by addition of sodium bicarbonate, but as the resulting solution is merely a mixture of sodium acetate and sodium salicylate, this method is not admissible. It is said that sodium citrate will dissolve acetylsalicylic acid without dissociation: for each grain of aspirin 4 grains of sodium citrate should be added. Such a solution, flavored with syrup of lemon, is suitable for administration to children.

The usual test for decomposition of acetylsalicylic acid is the detection of the freed salicylic acid by means of ferric chlorid solution. It occurred to me, therefore, that possibly such a test was used as a basis of the contention of the nondecomposition of acetylsalicylic acid in sodium citrate solution. If so, the seemingly negative reaction obtained

Results of Titration

Interval of Time	C.c. of N/1 NaOH Consumed by 20 c.c. of Solution
3 hours	8.0
1 day	9.4
2 days	10.7
3 days	11.35
3½ days	11.80
6 days	12.70
9 days	13.80
14 days	14.85
17 days	15.20
Complete hydrolysis	15.70

may be misinterpreted, because citric acid, and citrates, interfere with the sensitiveness of the test, and hence it would not be reliable in the case at hand. To test this hypothesis, a solution was made up and the rate of hydrolysis determined by titrating with normal alkali during stated intervals.

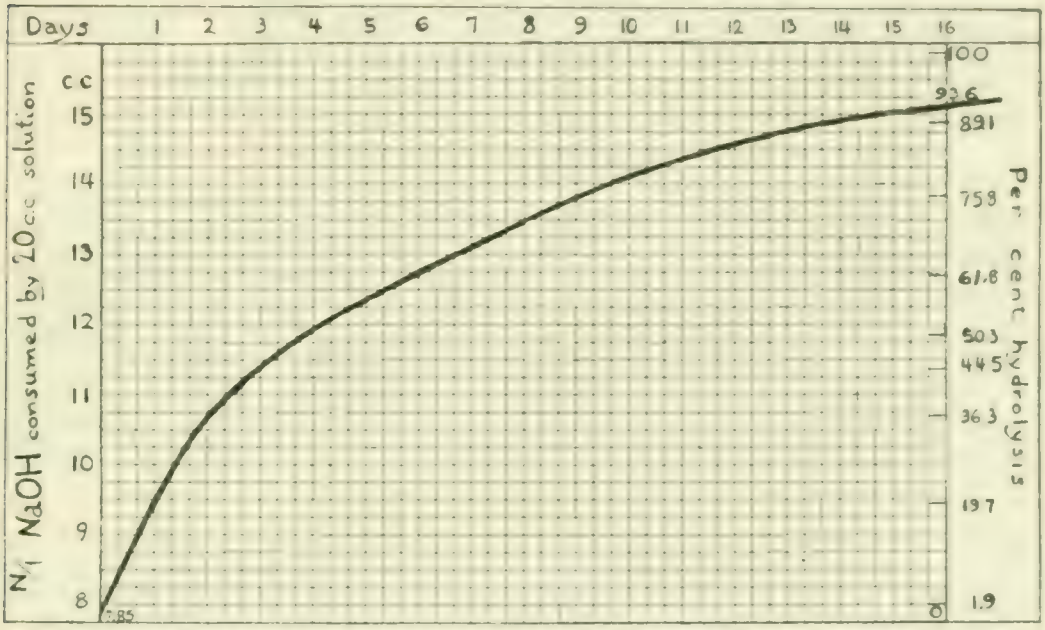
The solution was prepared by dissolving about 18 gm. of pure acetylsalicylic acid and 72 gm. of sodium citrate in 240 c.c. of water; after standing three hours it was filtered, and 20 c.c. used for the individual determinations. One teaspoonful of such a solution would represent about 5 grains of acetylsalicylic acid. The results of the titration will be found in the accompanying table. The solution was maintained at room temperature.

As will be noted in the accompanying chart, acetylsalicylic acid is hydrolyzed fairly rapidly in sodium citrate solution, over 50 per cent. decomposed in four days, and 75 per cent.

in nine days. Thus, a patient taking such a mixture which was 9 or more days old would be getting essentially the same ingredients as if sodium acetate and sodium salicylate had been used in place of the acetylsalicylic acid.

Obviously, the assertion that acetylsalicylic acid is not broken down to form salicylic acid and acetic acid (or their salts) is not based on scientific work.

The hydrogen ion concentration of the citrate solution alone was $p_H = 9.0$; after addition of acetylsalicylic acid, it was $p_H = 5.4$; after seventeen days it was $p_H = 4.6$. Thus it may be seen that the solution is appreciably acid, sufficient



Hydrolysis of acetylsalicylic acid in sodium citrate solution.

to decompose hexamethylenamin, with which it has been recommended to be dispensed.

Very recently 1 part of potassium citrate has been suggested in place of 4 parts of sodium citrate. Such a solution would hydrolyze, if anything, faster than one made with a higher concentration of the sodium salt.

CONCLUSION

It has been claimed that acetylsalicylic acid may be dispensed in a solution of sodium citrate without decomposition of the acetylsalicylic acid. The experiments here reported show that this is incorrect; that after four days the acetylsalicylic acid is broken down to the extent of 50 per cent.; after nine days, to 75 per cent., and that in seventeen days it is almost completely hydrolyzed.

PART II

REPORTS BASED ON ARTICLES WHICH APPEARED IN THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

WESTERN MEDICAL ASSOCIATION

Another Phenobarbital (Luminal) Mail-Order Treatment for Epilepsy

(Abstracted, with additions, from The Journal A. M. A., Jan. 28, 1922, p. 296)

The "Western Medical Association," Chicago, is selling a secret mixture on the mail-order plan for the alleged cure of epilepsy. Investigation seems to show that there are two men mainly concerned in operating the Western Medical Association, one Joseph B. Creevy and the other Dr. W. W. Lister. Creevy, it is said, had previously been connected with one of the smaller mail-order houses in Chicago. Lister is a physician.

THE JOURNAL has received many inquiries regarding the Western Medical Association and its treatment, some of them coming from the medical superintendents of state institutions for epileptics. One of these physicians wrote to the Western Medical Association and asked for information regarding the composition of this "treatment." In reply he received a letter from the "Association's Secretary" stating that "we do not wish to disclose the composition of our treatment for epilepsy." In the advertising, the firm decrys the use of bromids and extols the "Western Medical Association Treatment."

Because of the number of inquiries received it was deemed desirable by THE JOURNAL to determine the essential drugs in the "Western Medical Association Treatment" for epilepsy. It was a foregone conclusion that the essential drug was phenobarbital (luminal); since this drug has been found useful in the symptomatic treatment of epilepsy, those exploiting medical mail-order cures for epilepsy are using it to the exclusion of the bromid treatment.

LABORATORY FINDINGS

One original "Western Medical Association Treatment" was submitted to the A. M. A. Chemical Laboratory with the request that the active constituents be determined. The "treatment" is sold in three boxes, "*A*," "*B*" and "*C*," respectively.

A.—The box contained 30 white tablets, with directions to "Take one at bedtime and one in the morning." Each tablet weighed approximately 0.1 gm. (1½ grs.). They were found to contain phenobarbital (luminal), starch and a small amount of a substance having the microscopic characteristics of talc. The amount of phenobarbital present was 66.5 per cent., equivalent to 0.66 gm. (1 grain) phenobarbital in each tablet. Bromids were absent.

B.—The box contained 60 brownish tablets, with directions to "Take two in the morning and two at noon." The tablets responded to tests for calcium, magnesium (in small amount), lactate and phosphate; bromids were absent. Organic material was present. The tablets had the general appearance and taste of "Digestive Tablets" still sold by pharmaceutical houses. Such so-called digestive tablets generally have the formula: pepsin 1 gr., Pancreatin 1 gr., and Calcium lactophosphate 2 gr. These tablets, therefore, were tested for enzymic activity. There was noted a weak peptic activity, indicating the presence of pepsin. There was no positive reaction for pancreatin or diastase, indicating the absence of these substances at least in active form. Tests for epinephrin, thyroid and alkaloids were negative. The "*B*" tablets are essentially of the digestive type which contain pepsin and calcium lactophosphate.

C.—The box contained 30 yellow coated tablets, with directions to "Take one, two or three at night as necessary to move bowels freely." The tablets contain laxative drugs responding positively to tests for emodin-bearing drugs and for aloin.

As THE JOURNAL stated:

"Summed up then, 'this wonderful medicine,' which 'has been prescribed almost exclusively by world-renowned Specialists who command enormous fees,' is essentially phenobarbital (luminal) and a laxative."

Details of Analysis

Phenobarbital ("Luminal").—Phenobarbital was identified by its solubility in chloroform, and insolubility in water. Also when some of the powdered tablets were treated with sodium hydroxid solution, the substance dissolved; on acidification a white crystalline product was formed which was extracted with chloroform. The chloroform extract was evaporated to dryness; the residue melted at 171-172 C. A sample of known phenobarbital melted at 171-172 C. while a mixture of the two melted at the same temperature. (*a*) A sample weighing 0.3675 gram was shaken in a glass-stoppered flask with 20 c.c. of chloroform, and the chloroform solution filtered. The operation was repeated several times. The chloroform was evaporated by placing the beaker on an electric hot plate in a current of air caused by a nearby fan. The residue weighed 0.2437 gm., equivalent to 66.3 per cent. The residue was melted at 171-172 C., showing it not to be contaminated with other substances. (*b*) A sample weighing 0.6827 gm. yielded residue weighing 0.4597 gm., equivalent to 67.3 per cent.

WARN'S EPILEPSY TREATMENT

(Abstracted from The Journal A. M. A., March 18, 1922, p. 834)

In the Propaganda for Reform department of THE JOURNAL for Sept. 24, 1921, there appeared an article on "Maghee's Epilepsy Treatment," a mail-order affair operated by Thomas G. Maghee, M.D., Lander, Wyoming (See also Annual Reports A. M. A. Chemical Laboratory, Vol. 14 (1921), p. 36). The Warn's Remedy Company of Los Angeles, Calif., is in the same business as Maghee and there is a striking resemblance both in the products of the two concerns and their advertising methods.

Like the Maghee nostrum the "treatment" sells for $5. An order was sent for one "treatment" and the material turned over to the A. M. A. Laboratory. A summary of the laboratory report follows:

One original box of "Warn's Epilepsy Treatment" was submitted to the Chemical Laboratory for examination. The circular accompanying the box bore the statement: "A treatment containing no bromids, opiates or other narcotics or any habit forming drugs." In the box were 50 small sized

capsules, containing a powdered mixture of black color; the average content of each capsule was 0.093 gm. (1.4 grains). Qualitative tests indicated the presence of wood charcoal, phenobarbital (luminal) traces of iron, magnesium, calcium, potassium and sodium (these traces probably being derived from the charcoal). The amount of ash derived from the preparation was 3.5 per cent.; most of the ash consisted of silicon dioxid (sand). Quantitative determinations indicated the following:

Charcoal	28 per cent.
Phenobarbital (luminal)	72 per cent.

Each capsule of "Warn's Epilepsy Treatment" contains, essentially, 0.066 gm. (1 grain) of phenobarbital, to which has been added some charcoal. "Warn's Epilepsy Treatment" differs but slightly (by absence of bismuth subnitrate) from Maghee's Epilepsy Treatment, analyzed a few months ago.

Details of Analysis

The amount of material was so small that all work had to be done with smaller amounts than otherwise desirable.

Charcoal.—A weighed sample was extracted with chloroform in a Soxhlet apparatus. The residue was weighed as charcoal (see *a* and *b*). The black substance was treated first with 50 c.c. of hot 10 per cent. sodium hydroxid on a slow gooch, then washed, and then treated with 50 c.c. of concentrated hydrochloric acid, washed and dried. The loss in weight was 7 per cent. which was in keeping with non-carbon content of charcoal. The black material burned readily. (*a*) 0.7695 gm. left a residue after chloroform extraction weighing, after drying at 120 C., 0.2192 gm., equivalent to 28.4 per cent. (*b*) 0.9784 gm. left a residue weighing 0.2720 gm., equivalent to 27.8 per cent.

Phenobarbital.—After extraction of the sample with chloroform in the Soxhlet apparatus, the chloroform extract was evaporated to dryness, and then dried at 100 C. for three hours. (*a*) 0.7695 gm. yielded 0.5568 gm. of extract, equivalent to 72.3 per cent. (*b*) 0.9784 gm. yielded 0.7056 gm. extract equivalent to 72.1 per cent. In case of this extract, it was powdered and the melting point determined which was 173-174 C. (uncorrected). The melting point of a specimen of "luminal-Merck" (manufactured previous to the war) was 172-173 C. and a mixture of the two melted at 172.5-174 C. (uncorr.) which identified the product as phenobar-

bital. The extract dissolved in dilute sodium hydroxid solution; a precipitate formed when the solution was acidified.

EKSIP

(Reprinted, with slight modifications, from The Journal A. M. A., April 1, 1922, p. 991)

This is a mail-order "cure" for diabetes marketed by one Matthew Richartz. The advertising slogan of Richartz is: "No More Dieting! No More Starving! 'Eat and Get Well.'" According to the advertising matter, Eksip is the discovery of "the famous Dr. Stein-Callenfels." This famous individual, we are told, had wonderful success in treating diabetes with his discovery "Eksip." Unfortunately, "just as his fame was being spread throughout Europe" Stein-Callenfels died. On his deathbed he bequeathed Eksip to the brother of Matthew Richartz, who in turn has made Matthew the "sole proprietor and distributor of this valuable preparation in America."

Eksip comes in tablet form and the price asked is $6 for 200 tablets. The directions are to take two or three tablets a day:

> "When you order and take 'Eksip' as directed, no diet list whatever is given. You are directed to eat what you need and to take the tablets as directed—that's all."

The advertising booklet states that the diabetic may even eat candy if he feels impelled to! There is the usual batch of testimonials from laymen; there is also one from Dr. Edmund Kolb of New York City. No information is given regarding the composition of Eksip, except that the booklet states, uninformatively, that it is "a palatable compound of time honored medicinal herbs." A preliminary examination of Eksip was made in the A. M. A. Chemical Laboratory and the following report was published in THE JOURNAL:

"The bulk of the tablets consist of magnesium carbonate and starch. A small quantity of an unidentified drug was found. It was not determined whether this was of vegetable or animal origin. Alkaloids, heavy metals and emodin-bearing drugs were absent.

"The preparation is not identical with the Eksip (also a diabetic remedy) examined by Mannich and Kather in 1915 (*Ap. Ztg.*, **30**:240, 1915). This was a liquid containing an extractive from an unidentified drug and a considerable quantity of free hydrochloric acid."

LEAVEN'S ASTHMA PRESCRIPTION

(Reprinted with additions, from The Journal A. M. A., April 1, 1922, p. 991)

This preparation is put on the market by the Leavengood Drug Company, Rosedale, Kan.; Clyde Leavengood, president. Advertisements in newspapers that are not too particular about their advertising pages, notify the public: "Asthma Cured by Simple Remedy"; that a "famous druggist discovered this simple remedy." The "famous druggist" is Mr. C. Leavengood; he made the "discovery" thirty years ago.

"Mr. Leavengood feels so confident that his prescription will cure in all cases that he generously offers to send a big bottle on ten days' free trial."

In the advertising matter that is sent to those who answer the advertisement, one learns that the "discovery" of the "famous druggist" came about in this wise: Thirty years ago a man presented a prescription at the Leavengood Drug Store; the identity of the doctor who wrote the prescription "cannot be traced." The man was "CURED" and other asthma sufferers who heard of this and were unable to find the doctor "frantically sought the Leavengood Drug Store to get some of the medicine." The prescription had been lost but, fortunately for the sufferers—and Mr. Clyde Leavengood—the proprietor of the Leavengood Drug Store remembered the formula!

The usual batch of testimonials from laymen is forthcoming. There is also featured (in the approved "follow the arrow" style) an order for the nostrum sent in by Dr. A. L. Haight of Crystal Falls, Mich. Because of the number of inquiries about this product, an original specimen of "Leaven's Asthma Prescription" was submitted to the A. M. A. Chemical Laboratory for analytic purposes. The laboratory report follows:

"An original specimen of Leaven's Asthma Prescription was examined. The package contained about four fluidounces of a dark brownish-red, syrupy liquid, having a neutral reaction to litmus and an odor suggestive of a mixture of oils of sassafras and wintergreen. On evaporation of an ether extract of the preparation, a distinct odor like oil of spearmint was observed. The preparation had a harsh, disagreeable, but somewhat sweet, taste, resembling that of potassium iodid in syrup. Iodid, potassium, sucrose (cane sugar), a trace of iron and an unidentified yellow dye were detected by qualitative tests. Alcohol, alkaloids, ammonium

salts, heavy metals, emodin-bearing drugs, phosphates, salicylates, sodium salts and sulphates were absent. The absence of alkaloids excludes the presence in the preparation of such drugs as hyoscyamus and the opium derivatives, substances sometimes employed in the treatment of asthma.

"Quantitative examination indicated that the composition of Leaven's Asthma Preparation put out by the Leavengood Drug Company, Rosedale, Kansas, is essentially as follows:

"Potassium iodid .....10.9 gm.
"Sucrose (cane sugar).....55.0 gm.
"Iron .....a trace
"Water, flavoring and coloring matter to make 100 c.c."

THE JOURNAL commented as follows:

"It is evident from the analysis that a solution of about 48 grains of potassium iodid in a fluidounce of simple syrup would have whatever anti-asthmatic properties are possessed by 'the most remarkable asthma remedy ever known to mankind' discovered by the 'famous druggist' of Rosedale, Kansas."

Details of Analysis

Potassium Iodid.—Fifty c.c. of the preparation were diluted to 500 c.c. with distilled water and aliquot portions taken for examination. Ten c.c. of the diluted solution were acidified with nitric acid, silver nitrate soluton added and the silver iodid collected, dried and weighed in the usual way. The yield of silver iodid from 10 c.c. of the diluted solution was 0.1539 gm., equivalent to 10.8747 gm. of potassium iodid per 100 c.c. A duplicate of 10 c.c. gave 0.1546 gm. of silver iodid, equivalent to 10.9313 gm. of potassium iodid per 100 c.c. Average 10.903 gm. of potassium iodid per 100 c.c. Fifty c.c. of the diluted solution were heated in a Kjeldahl flask with diluted sulphuric acid and diluted nitric acid until the solution became colorless, more of the acids being added as required. After the mixture became colorless it was transferred to a weighed platinum dish, heated to dryness, the residue treated with a fragment of ammonium carbonate. again heated and the residue weighed as potassium sulphate. The weight of potassium sulphate obtained was 0.2848 gm., equivalent to 10.8526 gm. of potassium iodid per 100 c.c. The sulphate obtained above was determined by solution of the residue in water, filtration of the solution, addition of barium chlorid solution and weighing the barium sulphate

in the usual way. The weight of barium sulphate obtained was 0.3825 gm., equivalent to 10.881 gm. of potassium iodid per 100 c.c. of the original solution. The close agreement between the weights of potassium sulphate and barium sulphate obtained (after calculation to potassium iodid) excludes the presence in any appreciable quantities of sodium salts. The close agreement between the potassium iodid as calculated from silver iodid and that as calculated from potassium sulphate excludes the presence of chlorids in appreciable quantities.

Sucrose.—Fifty c.c. of the diluted solution were clarified by the addition of a slight excess of basic lead acetate solution, filtration, addition of sodium sulphate solution to the filtrate to precipitate the excess of lead and filtration to remove lead sulphate. The filtrate was diluted to 500 c.c. and the optical rotation observed in a 200 m.m. tube at 20 C. with sodium light. The rotation was 1.60° and 1.63° or a mean of 1.615°. This is equivalent to 55.04 gm. of sucrose per 100 c.c. of original solution.

QUEEN OF ANTISEPTICS

(Abstracted, with additions, from The Journal A. M. A., April 8, 1922, p. 1072)

This preparation is marketed by a person in Aurora, Ill., calling herself "Mme. Leonard." The following claims appear on the label:

"A Perfect Vaginal Germ Destroying Powder and Applicator.
"Antiseptic, Anodyne Adhesive, Astringent.
"Action instantaneous and lasting, non-irritating, scientifically prepared. Use as directed."

The preparation comes in a package containing approximately 79 grams (about 2¾ ounces) and is in the form of a white, odorless powder. It was recently examined in the A. M. A. Chemical Laboratory and the following report published in THE JOURNAL:

"The material was not completely soluble in water or in alcohol. The portion of the substance soluble in alcohol responded to tests for boric acid. This portion contained neither mercuric chlorid, salicylic acid, benzoic acid nor chinosol, substances frequently used as antiseptics. Such

astringents as ferric chlorid and tannic acid were absent. The part insoluble in alcohol gave tests for a mercury compound, a chlorid and ammonia. This indicated the presence of ammoniated mercury. Quantitative analysis showed that the preparation is composed essentially as follows:

"Boric acid .....97 per cent.
"Ammoniated mercury ..... 3 per cent."

The 2¾ ounce package of Mme. Leonard's "Queen of Antiseptics" sells for $2.00; the approximate cost of materials (1922 prices) is 2½ cents.

Details of Analysis

Boric Acid.—Some of the material was shaken with alcohol and the mixture filtered. On ignition the filtrate burned with a green-mantled flame. An aqueous extract of the powder was acidified with hydrochloric acid and a piece of turmeric paper moistened with the solution. On drying, the paper became reddish brown. This became greenish black on moistening with ammonia water.

Boric acid was approximately determined by direct titration of the alcoholic extract from a weighed portion of the material with normal sodium hydroxid in presence of glycerin, using phenolphthalein as indicator, as described in the U. S. P. IX, p. 9. About 1 gm. was weighed, the powder stirred for some time with 100 c.c. of neutral alcohol, the insoluble part collected in a weighed Gooch crucible, dried at 80 C. and weighed as ammoniated mercury (See ammoniated mercury below). The alcoholic filtrate from 1.0008 gm. of material required 15.657 c.c. of normal sodium hydroxid, equivalent to 0.971047 gm. of boric acid, or 97.027 per cent. A duplicate of 1.0339 gm. of material required 16.17 c.c. of normal alkali, equivalent to 1.00286 gm. of boric acid or 97.00 per cent. Average 97.01 per cent. of boric acid.

Ammoniated Mercury.—The alcohol insoluble material obtained in the determination of boric acid (see above) was dried and weighed. From 1.0008 gm. of material 0.0302 gm. of alcohol-insoluble material was obtained, equivalent to 3.017 per cent. From 1.0339 gm. of material 0.0317 gm. of insoluble material was obtained, equivalent to 3.066 per cent. A third weight of 5.0026 gm. gave 0.1488 gm. of insoluble material, or 2.974 per cent. Average 3.019 per cent. of alcohol-insoluble material.

Ammoniated mercury was also determined by distilling a weighed quantity of the material with an excess of sodium hydroxid solution, the liberated ammonia being collected in a measured excess of normal hydrochloric acid. The excess acid was then titrated with normal sodium hydroxid, alizarin red being used as indicator. The distillate from 9.9585 gm. consumed 1.1195 c.c. of normal hydrochloric acid, equivalent to 0.301247 gm. of mercurammonium chlorid, or 3.02 per cent.

Ammoniated mercury was also determined electrolytically by calculations from the amount of mercury deposited from a solution of the alcohol-insoluble part in diluted nitric acid. The alcohol-insoluble part, together with the asbestos in the Gooch crucible, was dissolved so far as possible in diluted nitric acid, the solution filtered to remove asbestos and the solution electrolyzed, the mercury being deposited in a weighed platinum dish. The deposited mercury was dried over sodium hydroxid in an atmosphere containing mercury vapor. The weight of mercury obtained was multiplied by the factor 1.256 to obtain the weight of ammoniated mercury in the original material. The mercury obtained from 5.0026 gm. of original material weighed 0.1190 gm., equivalent to 0.149535 gm. of ammoniated mercury, or 2.99 per cent.

As a check on the method described above, a weighed quantity of the material was suspended in 250 c.c. of water, the mixture acidified with hydrochloric acid, warmed and hydrogen sulphid passed in to saturation. The precipitated mercuric sulphid was collected on a filter, washed with alcohol, then with carbon disulphid, dried at 100 C. and weighed. In one test (A) from 2.2514 gm. of material, 0.0626 gm. of mercuric sulphid was obtained, equivalent to 0.067817 gm. of ammoniated mercury, or 3.013 per cent. In another test (B) 0.2868 gm. of mercuric sulphid was obtained from 10.2602 gm. of material, equivalent to 0.310748 gm. of ammoniated mercury, or 3.028 per cent. Average 3.022 per cent.

Alkaloids.—Some of the material was suspended in water, an excess of ammonia water added and the mixture shaken with a mixture of chloroform and ether. The solvent was evaporated, the residue (which was but a trace) was taken up in water, the solution acidulated with hydrochloric acid and the usual alkaloidal reagents applied to the solution. The results were negative. The presence in the preparation of such drugs as quinin, cocain and morphin was thus eliminated.

KOLOR-BAK

(Abstracted, with additions, from The Journal A. M. A., April 15, 1922, p. 1146)

A Hair Dye Exploited by Direct and Inferential Falsehood

"Kolor-Bak" is put on the market by the Hygienic Laboratories of Chicago, successors to the "Kolor-Bak Products Co." Here are some of the claims made for this preparation:

"Kolor-Bak is in no sense a dye or stain."

". . . restores gray hair to the original color, no matter what it may have been; whether brown, auburn, red, blonde or black."

"It is positively harmless . . . none of the injurious effects of many hair preparations can result from Kolor-Bak."

". . . nor is it one of those 'hair restorers' containing powerful mineral ingredients. . . ."

". . . to restore gray hair to its original color we must repair the pigment supply. That is what 'Kolor-Bak' does."

"It stimulates the papilla to increased pigment production. . . ."

Probably because of the wide advertising campaign of this concern, THE JOURNAL, during the past year or two, has received a very large number of inquiries regarding it. It was finally decided to analyze the product. Specimens were purchased, were analyzed, and the following report published in THE JOURNAL:

"Specimens of Kolor-Bak, sold by the Hygienic Laboratories of Chicago, were examined. The presence of 5 per cent. of alcohol is declared on the label and the preparation is stated 'to be free from nitrate of silver, mercury, or any other ingredients injurious to the hair or scalp.' No other information concerning its composition was given. Kolor-Bak was found to be a colorless liquid containing a considerable quantity of a pale yellow powder, which resembled precipitated sulphur. The preparation had a slight acetous odor, an acid reaction and was faintly perfumed.

"Qualitative tests demonstrated the presence of precipitated sulphur, a lead salt, an acetate, a chlorid, a sodium salt, alcohol, glycerin and traces of a sulphate and of a calcium salt. Borax, cantharides, hydrogen peroxid, silver salts, mercury salts, pilocarpin, paraphenylendiamin or quinin—substances sometimes found in 'hair dyes' or 'hair tonics'—were absent, as also were nitrates, phosphates and carbonates.

"Analysis indicated that different specimens of Kolor-Bak differed considerably in quantitative composition. Accordingly three separate specimens of Kolor-Bak were examined

and the average results obtained in the analyses recorded. According to the analyses the composition of Kolar-Bak (in grams per 100 c.c.) is essentially as follows:

"Lead acetate, U. S. P. (sugar of lead)	0.69 gm.
"Precipitated sulphur	1.00 gm.
"Lead chlorid	0.16 gm.
"Lead oxid (litharge)	0.20 gm.
"Sodium chlorid (common salt)	0.60 gm.
"Glycerol	2.00 gm.
"Alcohol, by volume	4.8 per cent.
"Water, sufficient to make	100 c.c.

"The analytical results show that Kolor-Bak is a lead and sulphur wash. It is probable that lead chlorid was not a constituent of the formula for the preparation but that this compound was formed by interaction between the lead acetate and the sodium chlorid after the ingredients were mixed. Although the label declares that the preparation is free from 'any ingredients injurious to the hair or scalp,' Kolor-Bak contains lead acetate, a substance which is distinctly poisonous."

Concerning the claims made for Kolor-Bak and the use of lead salts in hair dyes THE JOURNAL commented as follows:

"From the chemists's report it is obvious that each and every one of the claims quoted at the beginning of this article is specifically false. Kolor-Bak *is* a dye; it does *not* 'restore gray hair to the original color'; it is *not* 'positively harmless'; it *is* 'one of those hair restorers containing powerful mineral ingredients'; it does *not* 'repair the pigment supply,' nor does it 'stimulate the papilla to increased pigment production.'

"Medical literature contains references to cases of poisoning from hair dyes containing lead salts, and most standard books on therapeutics and pharmacology refer to this fact. In Peterson and Haines' 'Text-Book on Legal Medicine and Toxicology' in the chapter on chronic lead-poisoning we read:

"'Most of the lotions called "hair-renewers" are preparations containing sulphur and lead acetate or calcium plumbite. They do not restore the natural pigment, but cause the precipitation of black lead sulphid in the hair structure, so as to simulate the natural color.'"

Details of Analysis

Water-Insoluble.—Since Kolor-Bak is a mixture of a solution and heavy, insoluble solids, it was a difficult matter to

obtain uniform samples for analysis. In one test (*a*) a mark was placed on the neck of an entire bottle of Kolor-Bak and the contents decanted through a weighed Gooch crucible.

Reproduction (reduced) of an advertisement for Kolor-Bak.

The bottle was washed with water and the washings poured through the crucible. After drying the bottle, the content was determined by pouring in water from a measuring con-

tainer until the mark on the neck was reached. The contents of this bottle were 247 c.c. In two other tests (*b* and *c*) the contents of two other bottles were shaken (separately) to obtain as uniform a mixture as possible, and 100 c.c. were taken from each bottle. The analysis was thus conducted in each of the three specimens and the mean values found, taken as representative. The water-insoluble residues were dried at 100 C. and weighed. The insoluble residue from 247 c.c. weighed 4.1359 gm., equivalent to 1.6744 gm. per 100 c.c. The residue from "b" weighed 1.2243 gm. and that from "c," 0.9959 gm. Average, 1.2982 gm. per 100 c.c.

Chloroform-Insoluble.—The Gooch crucible containing the water-insoluble residue was placed in a Soxhlet extraction apparatus and the residue extracted with chloroform until exhausted. The insoluble residue was dried and weighed. The insoluble portion from 247 c.c. of Kolor-Bak weighed 0.9968 gm., equivalent to 0.4035 gm. per 100 c.c. of original material. The residue from 100 c.c. weighed 0.3490 gm.; a duplicate weighed 0.2409 gm. Average, 0.3312 gm. for 100 c.c.

Sulphur.—The chloroformic extract obtained as above was evaporated to dryness, the residue dried at 80 C. and weighed. The sulphur from 247 c.c. of original material weighed 3.0565 gm., equivalent to 1.2374 gm. per 100 c.c. The sulphur from 100 c.c. weighed 0.8810 gm.; a duplicate weighed 0.7610 gm. Average, 0.9598 gm. per 100 c.c.

Lead Oxid and Lead Chlorid.—The residue in the Gooch crucible remaining after the extraction with chloroform (together with the asbestos mat) was suspended in water and treated with hydrogen sulphid to transpose the lead chlorid and lead oxid in the residue to lead sulphid. The lead sulphid was collected on a filter and the filtrate reserved for determination of chlorid. The lead sulphid was dissolved in hot, dilute nitric acid, the solution filtered, the filtrate evaporated to small volume in the presence of an excess of sulphuric acid, about one-third volume of alcohol added and the mixture allowed to stand over night. The precipitated lead sulphate was collected in a weighed Gooch crucible, dried at 100 C. and weighed. The lead sulphate from the chloroform-insoluble residue from 247 c.c. of original material weighed 1.1493 gm., equivalent to 0.7833 gm. of lead, or 0.317132 gm. of lead per 100 c.c. The lead sulphate from a similar residue from 100 c.c. of material weighed 0.3959 gm., equivalent to 0.270518 gm. of lead. A duplicate of 100 c.c. under similar treatment gave 0.2681 gm. of lead

sulphate, equivalent to 0.183193 gm. of lead. Average, 0.256947 gm. total lead in chloroform-insoluble. The filtrate from the lead sulphid as obtained from the chloroform-insoluble material was placed in a reflux apparatus which was connected with an aspirator. The liquid was boiled to remove hydrogen sulphid, the hydrochloric acid (which had been liberated from the lead chlorid) being condensed and returned to the flask through the reflux. The liquid in the reflux was acidulated with nitric acid, an excess of silver nitrate added, and the silver chlorid collected, dried and weighed in the usual way. The silver chlorid obtained from the chloroform-insoluble residue from 247 c.c. of original material weighed 0.4279 gm., equivalent to 0.414977 gm. of lead chlorid, or 0.1680 gm. per 100 c.c. This is equivalent to 0.125148 gm. of lead per 100 c.c. originally present as lead chlorid. The silver chlorid obtained as above described from 100 c.c. of original material weighed 0.1640 gm., equivalent to 0.112061 gm. of lead originally present as lead chlorid. A duplicate of 100 c.c. of original material gave 0.1010 gm. of silver chlorid, equivalent to 0.06693 gm. of lead originally present as lead chlorid. Average, 0.101379 gm. of lead as chlorid. The lead in the chloroform-insoluble residue which was present as lead chlorid (0.101379 gm.) was subtracted from the total lead in the chloroform-insoluble residue (0.266947 gm.). The remainder (0.155568 gm.) is the lead which is present in this residue as lead oxid. This is equivalent to 0.167585 gm. of lead oxid per 100 c.c. of original material.

Lead Acetate.—The filtrate and washings obtained by filtering the original material was treated with hydrogen sulphid in the cold. The precipitated lead sulphid was dissolved in hot dilute nitric acid, the solution filtered to remove free sulphur, the filtrate evaporated to small volume in the presence of an excess of sulphuric acid, about one-third volume of alcohol added and the mixture allowed to stand over night. The lead sulphate was collected in a weighed Gooch crucible, dried and weighed in the usual way. The lead sulphate from 247 c.c. of original material weighed 1.2288 gm., equivalent to 0.6222 gm. of crystallized lead acetate per 100 c.c. of original material. The lead sulphate from 100 c.c. of original material weighed 0.4600 gm., equivalent to 0.5754 gm. of lead acetate U. S. P. per 100 c.c. A duplicate of 100 c.c. gave 0.5071 gm. of lead suphate, equivalent to 0.6338 gm. of lead acetate U. S. P. Average, 0.6106 gm. of lead acetate U. S. P. per 100 c.c. of original material.

Sodium chlorid.—The filtrate from the water-soluble portion of the material after removal of the lead sulphid by filtration was boiled in a reflux apparatus which was connected with an aspirator. The hydrogen sulphid was removed by boiling, the acetic acid (and perhaps traces of hydrochloric acid) being condensed and returned to the boiling flask. After cooling, the solution was made up to 1,000 c.c. (or to 250 c.c.) and aliquot portions taken for various determinations. Chlorid was determined in 25 c.c. of the solution by weighing as silver chlorid in the usual way. Twenty-five c.c. of the solution obtained from 247 c.c. of the original material gave 0.0937 gm. of silver chlorid and a duplicate gave 0.0948 gm. of silver chlorid; average, 0.09425 gm. of silver chlorid. This is equivalent to 0.62274 gm. of sodium chlorid per 100 c.c. of original material. Ten c.c. of a solution, obtained from 100 c.c. of original material diluted to 250 c.c., gave 0.0502 gm. of silver chlorid and a duplicate gave 0.0495 gm. of silver chlorid. Average, 0.04985 gm. of silver chlorid, equivalent to 0.50847 gm. of sodium chlorid per 100 c.c. of original material.

Glycerol.—Glycerol was approximately determined in aliquot portions of the diluted, lead-free solution (as obtained under "sodium chlorid") by the following method:

An aliquot portion of the solution was evaporated to small volume on a slowly simmering steam bath, the residue taken up in four volumes of alcohol and an equivalent volume of ether added. After standing over night, the mixture was filtered, the residue washed with a mixture of equal volumes of alcohol and ether and the filtrate evaporated in a weighed platinum dish to small volume on a slowly simmering steam bath. The residue was dried over sulphuric acid for several days with occasional agitation by tipping the dish to an inclined position, and weighed. The dish and contents were then heated to remove organic material and the dish and ash content again weighed. The loss is calculated as glycerol.

The glycerol from 250 c.c. of the diluted solution, representing 61.75 c.c. of original material, weighed 1.3297 gm., equivalent to 2.1137 gm. per 100 c.c. of original material. The glycerol from 100 c.c. of solution, representing 40 c.c. of original material, weighed 0.8297 gm., equivalent to 2.0744 gm. per 100 c.c. of original material. Average, 2.0941 gm. of glycerol per 100 c.c. of original material.

Calcium sulphate.—An aliquot portion of the solution, such as had been used for the determination of glycerol, was

tested for calcium and for sulphates by the usual reagents. Both substances were present in very small amounts. From this it was surmised that an impure water such as hydrant water or river water had been used in preparing Kolor-Bak.

PLATT'S CHLORIDES: DECEPTION OR IGNORANCE?

(Reprinted from The Journal A. M. A., July 22, 1922, p. 319)

An advertisement for Platt's Chlorides calls attention to the fact that chlorin antiseptics are at present in favor. The statement is then made that "chlorid of lime" is perhaps the best known of the older chlorin antiseptics. To quote:

> "As prepared and combined (with other related salts) under the name of Platt's Chlorides it ["chlorid of lime"] has served well for years for disinfection purposes about the house. Platt's Chlorides is still the choice of a great many discriminate [*Sic!*] people and is to be found in homes and in hospitals everywhere. In fact, with our present appreciation of chlorin, this preparation is sure to win more friends than ever before."

"Chlorid of lime" is an unscientific name for calcium hypochlorite or chlorinated lime (the pharmacopeia gives it as a synonym for *calx chlorinata*). An analysis of Platt's Chlorides made several years ago in the A. M. A. Chemical Laboratory failed to show any active (free) chlorin derivative. True chlorids were present, but chlorin in the negatively charged (combined) form as in chlorid (Cl^-) is not known to have any germicidal effects; it is active only when it is in a positively charged form as in the free state ($^-Cl—Cl^+$) or in hypochlorites and derivatives (HO^-Cl^+). A recent specimen of Platt's Chlorides has also been tested for hypochlorites. The chemical laboratory again reports the absence of active chlorin (Cl^-) compounds; further it points out that hypochlorite could not be present as the product contains considerable iodid which would be incompatible with hypochlorite.

The question naturally arises: Is this misinformation concerning Platt's Chlorides a case of deception or is it merely ignorance due to the fact that the household phrase "chlorid of lime" resembles the name calcium chlorid, the latter being present in Platt's Chlorides? The evidence points to deception because the label on the bottle states (in accordance with the requirement of the federal law) that calcium chlorid in Platt's Chlorides is *inert* material!

Platt's Chlorides has been the subject of previous reports. The Council on Pharmacy and Chemistry declared it "inadmissible to New and Nonofficial Remedies because its composition is uncertain and indefinite and because the claims made for it are exaggerated and misleading."

GRAHAM'S NEUTROIDS

The Latest Thing in the Obesity Cure Line

(Abstracted, with additions, from The Journal A. M. A., Sept. 30, 1922 p. 1163)

During the past month or two THE JOURNAL has received scores of inquiries from physicians and laymen regarding an alleged cure for obesity put out by one R. Lincoln Graham, M.D., of 123 E. 89th St., New York City.

STUFF AND GROW THIN

Graham claims to be head of "the famous Graham Sanitarium" of New York City, where it is said experiments have disclosed "secrets which scientists have sought for years." These "secrets," it seems, comprise a method by which the obese, though gluttonous and lazy, may reduce without abandoning either gluttony or laziness! To quote:

> "Are you fond of sweets? Do you enjoy the foods which have always been thought fattening in the past, such as fat meats, rich gravies, desserts, etc.? Are you a hearty eater?
>
> "Then you will be glad to learn that you may now indulge your appetite to the fullest extent. You may eat all the fats, starches and sweets you wish. You may eat as heartily as you please and as often as you desire. There is absolutely no need to restrict yourself.
>
> "If you have been taking any strenuous exercises in order to reduce, you may abandon them. They are not needed and if carried to excess they might even be harmful."

Graham, we are told, has discovered the "real cause of fat":

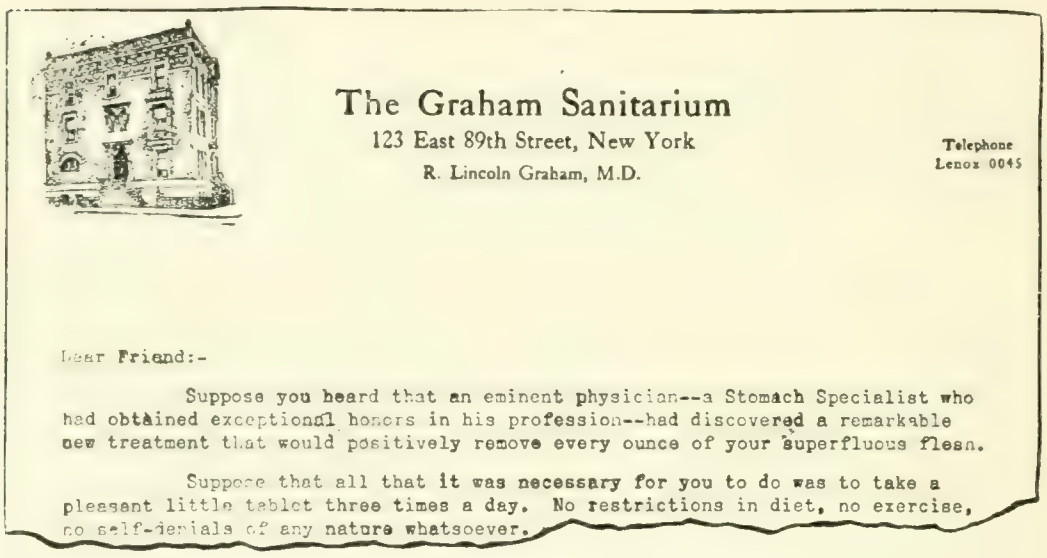
> "Dr. Graham's discoveries show that obesity is brought about by an over development of alcohol in the digestive tract."

After Graham had "discovered the real cause of this life-sapping, disfiguring obesity" his next effort, naturally was to devise a remedy that "would neutralize this alcoholic formation." Thus we read:

"Dr. Graham is known both in America and Germany as an authority on Materia Medica. His lectures and writings on medical subjects are studied by Medical Colleges, Medical Societies and physicians in both hemispheres. Therefore, his special knowledge along such lines enabled him, after some lengthy experiments, to devise a remedy made of harmless ingredients which would neutralize and finally prevent the formation of alcohol without interfering in the slightest degree with the digestive system, and without affecting the rest of the body."

THE TESTIMONIAL GAME

And, of course, the public has no means of estimating the truthfulness of these claims. Graham's marvelous remedy is known as "Neutroid Tablets." Like most "patent medicine" exploiters he makes a pretense of telling the public



The Graham Sanitarium
123 East 89th Street, New York
R. Lincoln Graham, M.D.

Telephone
Lenox 0045

Dear Friend:-

Suppose you heard that an eminent physician--a Stomach Specialist who had obtained exceptional honors in his profession--had discovered a remarkable new treatment that would positively remove every ounce of your superfluous flesh.

Suppose that all that it was necessary for you to do was to take a pleasant little tablet three times a day. No restrictions in diet, no exercise, no self-denials of any nature whatsoever.

Reduced reproduction of the opening paragraphs of the form letter sent out to the obese by the "Graham Sanitarium."

something about the composition of his nostrum. He publishes what purports to be the "opinions of leading physicians and chemists who have analyzed Dr. Graham's 'Neutroid Tablets.'" The first of these "opinions" is credited to one "Dr. Edwin F. Bowers . . . well known author and lecturer on medical subjects." To those familiar with the history of nostrum exploitation, any testimonial by Bowers should arouse suspicion. Bowers calls himself an M.D., but the American Medical Association's records of graduate and licensed physicians, the most complete extant and based on official data, fail to show that Edwin F. Bowers has ever been graduated by a reputable medical school or is entitled to write M.D. after his name; neither do we find any record of Bowers being licensed to practice medicine anywhere in the United States. Bowers is the gentleman who published an article in *Physical Culture* telling how locomotor ataxia

could be cured with a milk diet. Some laymen who wrote to Bowers regarding this "treatment" were told that the data were secured at Macfadden's sanatorium; they were told, too, that the Bioxal Chemical Company of New York City "put out a treatment for ataxia and kindred troubles" called "Bioplasm." At that time the president of the Bioplasm Company was one Edwin F. Bowers.

Another testimonial is from Mr. E. H. Gane, Chief of the Scientific Department of McKesson and Robbins. Mr. Gane should know better! Possibly his testimony is due to the exigencies of commercialized pharmacy. A third testimonial is by a "Dr. Henry J. Swoboda, Bacteriologist and Analytical Chemist." We are unable to find any record of Dr. Swoboda either as a physician or as a member of the American Chemical Society.

Bowers, in his testimonial, claims to have found three ingredients in Neutroid Tablets, one of which, according to him, "could be taken by the pound without harm." Another "could be taken in any amount," while the third "one could take at one time a quantity thirty-seven times as large as is contained in one of these tablets." Graham himself declares that his nostrum contains "no thyroid extract, no free iodids . . . or harmful drugs of any kind."

Specimens of Dr. Graham's Neutroids were examined in the Laboratory and the following report published in THE JOURNAL:

The weight of Dr. Graham's Neutroids tablets averaged 0.295 gm. or about 4.6 grains. The odor of the tablets was disagreeable, somewhat like iodin or pyrrol. In the booklet describing the preparation there is no information concerning the ingredients of Neutroids, but much space is devoted to an explanation of what the nostrum does not contain. For example, it is stated on the authority of one Swoboda, who is said to be a bacteriologist and analytical chemist, that "Neutroid Tablets are free from thyroid extract, opium, or its alkaloids morphin and codein, cocain, belladonna and chloral hydrate."

The tablets were nearly insoluble in water but partially soluble in alcohol, ether and chloroform. Alkaloids, ammonium salts, boric acid, emodin-bearing drugs, milk sugar, nitrates, sulphates, zinc salts and phenolphthalein were absent. Starch and an insoluble substance, probably talc, were present in small amounts and a trace of iron was detected. The bulk of the tablets consisted of magnesium

carbonate and an organic iodin compound which responded to tests for iodol, although the product was not pure.

Quantitative analysis indicated that the composition of Neutroids is essentially as follows:

Iodol (impure)	50 per cent.
Magnesium carbonate	43 per cent.
Starch	4 per cent.
Talc	3 per cent.
Iron	Trace

Iodol is a combination of iodin with pyrrol, containing nearly 89 per cent. of iodin. It was described in the U. S. Pharmacopeia VIII, but was dropped in the last edition. It is official in some foreign pharmacopeias. It has been used chiefly as a substitute for iodoform. Iodol is distinctly poisonous, even when applied externally and a number of cases of poisoning are recorded. According to the United States Dispensatory, iodol, if given in sufficient doses to animals "causes emaciation, albuminous urine, fall of temperature, general loss of muscular power and finally death from fatty degeneration of the liver and kidneys." To state that a nostrum containing iodol is "non-toxic" is false.

Concerning the preparation the methods used in its exploitation THE JOURNAL commented as follows:

"The exploitation of R. Lincoln Graham's 'Neutroids' follows the classical course of nostrums of this type: First, the buncombe regarding the alleged qualifications of the 'discoverer'; then the falsehood that the patient can indulge his appetite to the fullest extent and need not exercise; next the testimonial hocus and, finally, the claim that the 'cure' is harmless. Altogether, the product and its exploitation seem to conform strictly to the tenets of the 'obesity cure' business."

Details of Analysis

Alkaloids.—A portion of the material was percolated with water. The percolate gave no reactions when tested with the usual alkaloidal reagents. Some of the material was macerated with very dilute hydrochloric acid and the mixture filtered. The filtrate gave no reactions for alkaloids by treatment with the usual alkaloidal reagents.

Amidopyrin.—A portion of the material was percolated with water. The percolate gave no colored reactions with ferric chlorid solution or by platinic chlorid solution. This was taken to demonstrate the absence of amidopyrin.

Alphanaphthylamin and Betanaphthol.—The absence of any colored reaction on the treatment of the aqueous percolate (obtained as above) with ferric chlorid solution was taken to indicate the absence of alphanaphthylamin and betanaphthol.

Iodol (Tetraiodopyrrol).—For qualitative tests about 1 gm. of the material was shaken with the alcohol, the mixture filtered and about 1 c.c. of the filtrate taken for each test. A portion of the alcoholic solution was evaporated to dryness and the residue ignited. An abundance of iodin was given off in the form of violet vapors. The residue which remained was small. It responded to the tests for a magnesium compound. Another portion of the alcoholic filtrate was warmed with a few drops of nitric acid. A deep red color developed. Another portion was treated with an excess of a saturated solution of silver nitrate in alcohol. A blackish-green precipitate was produced and the mixture gave an almost colorless solution on being filtered. Another portion was evaporated to dryness and the residue warmed with sodium hydroxid solution and zinc dust. An odor like pyrrol was produced and a pine shaving moistened with hydrochloric acid and held in the vapors became a deep, purplish-red color. Another portion of the alcoholic solution was evaporated to dryness and the residue treated with sulphuric acid. A dirty green color developed which changed to violet and finally to brown. From these tests it was concluded that the major portion of the alcoholic extract of the tablets consists of iodol (tetraiodopyrrol).

The residue remaining after the extraction by alcohol was washed with ether and dried at 70 C. It was then treated with warm, very dilute hydrochloric acid and filtered. A portion of the acid filtrate was treated with hydrogen sulphid with negative results. On being made alkaline, it darkened, indicating the presence of iron or some metal of the iron group. Another portion of the acid filtrate was made alkaline with ammonia water, heated to boiling and filtered. A small quantity of a brown precipitate remained on the filter. This was dissolved in dilute hydrochloric acid and a few drops of potassium sulphocyanate solution added. A red color developed, indicating the presence of iron in small amount. The alkaline filtrate from the iron separation was treated with calcium oxalate solution with negative results. Sodium phosphate solution was then added. A white crystalline precipitate resulted, indicating the presence of a magnesium compound.

The residue remaining after the alcohol-insoluble residue had been treated with dilute hydrochloric acid was washed with water and examined with the microscope while still moist. Starch was identified and another substance occurring as fine, white, opaque particles was observed. On heating a portion of the material, such as was examined under the microscope, the organic matter was destroyed and an ash remained which appeared to have the properties of talc.

The quantitative determinations for iodin were made on the ether extracts and the alcoholic extracts obtained in the first stages of the determination for starch, talc and magnesium carbonate. A weighed portion of the material was percolated with ether, the percolate evaporated, the residue dried over sulphuric acid and weighed. From 1.0017 gm. an ether-soluble residue of 0.4501 gm. was obtained or 44.93 per cent. A duplicate of 1.0971 gm. gave 0.4809 gm. of ether-soluble residue, equivalent to 43.83 per cent. Average, 44.36 per cent. of ether extract.

Total Iodin.—The ether extract from the tablets was heated with an excess of nitric acid and solid silver nitrate. The silver iodid was collected, dried and weighed in the usual way. The silver iodid obtained from the ether extract from 1.0017 gm. of original material (0.4501 gm. ether extract) weighed 0.5020 gm., equivalent to 0.27123 gm. of iodin, or 60.26 per cent. Another ether extract was heated with 50 per cent. sulphuric acid and an excess of ferric ammonium sulphate and the liberated iodin distilled into a weak aqueous solution of potassium iodid. The free iodin was then titrated with tenth-normal sodium thiosulphate. The liberated iodin from the ether extract from 1.097 gm. of original material (0.4809 gm. of ether extract) required 26.76 c.c. of tenth-normal sodium thiosulphate, equivalent to 72.3 per cent. of iodin, calculated to the weight of ether extract. A duplicate of 0.9667 gm. of ether extract (from 2.2659 gm. of original material) required 52 c.c. of tenth-normal sodium thiosulphate, equivalent to 68.27 per cent. of iodin calculated to the weight of ether extract. Theory for pure iodol is 88.96 per cent. of iodin. The extract which was obtained by percolating the ether-insoluble residue with alcohol contained both iodin and magnesium. Evidently the alcoholic extract is a decomposition product formed by the action of alkaline magnesium carbonate on the unstable iodol. The iodin in the alcoholic extract was determined by heating with nitric acid and an excess of silver nitrate, collecting, drying and weighing the silver iodid in the usual way. An extract weighing

0.0616 gm. (obtained from 1.0017 gm. of original material) gave 0.0853 gm. of silver iodid, equivalent to 74.82 per cent. of iodin, based on the weight of alcoholic extract obtained. Magnesium was determined in the alcohol-soluble fraction by adding an excess of hydrochloric acid to the filtrate after filtering out the silver iodid, filtering to remove silver chlorid, precipitation of the magnesium by sodium phosphate in the usual way and weighing as magnesium pyrophosphate. The total of ether-soluble material and alcohol-soluble is equivalent to a little more than 50 per cent. of the total material (44.36 per cent. + 6.01 per cent. = 50.37 per cent). Therefore it is assumed that about 50 per cent. of the original weight of the tablets was composed of iodol.

The insoluble residue from the ether extract was dried at 60 C. to remove excess of solvent and extracted with alcohol. The solution was evaporated to dryness; the residue dried over sulphuric acid and weighed. From 1.0017 gm. of original material, a residue of 0.0616 gm. was obtained, equivalent to 6.15 per cent. A duplicate of 1.0971 gm. gave 0.0645 gm. of residue, equivalent to 5.88 per cent. Average, 6.01 per cent.

Talc and Starch.—The residue insoluble in ether and alcohol was dried at 70 C. and weighed. The ether-alcohol-insoluble residue was treated with warm, very dilute hydrochloric acid, the acid insoluble residue collected in a Gooch crucible and washed well with water, dried and weighed. This residue was considered as a mixture of starch and talc. The filtrate and washings were reserved. The acid insoluble residue was ignited and the noncombustible residue weighed as talc, the loss being considered as starch. The loss on heating from 1.0252 gm. of original material was 0.0380 gm., equivalent to 3.71 per cent. of starch. A duplicate of 0.9415 gm. gave 0.0381 loss at this stage, equivalent to 4.05 per cent. of starch. Another sample weighing 0.9736 gm. gave 0.0379 gm. of loss, equivalent to 3.89 per cent. of starch. A fourth sample (from a different lot of tablets) weighing 1.0971 gm. lost 0.0403 gm., equivalent to 3.77 per cent. of starch. The average of the four determinations is 3.85 per cent. of starch. From a weight of 1.0252 gm. of original material, a residue of 0.0258 gm. of acid-insoluble incombustible material was obtained, equivalent to 2.52 per cent. of talc. A duplicate of 0.9415 gm. of original material gave 0.0255 gm. of acid-insoluble noncombustible material, equivalent to 2.71 per cent. of talc. A third sample weighing 0.9736 gm. gave 0.267 gm.

of acid-insoluble noncombustible residue, equivalent to 2.74 per cent. of talc. A fourth sample (from a different lot of tablets) weighing 1.0971 gm. gave an insoluble residue of 0.210 gm., equivalent to 1.91 per cent. of talc. The average of the four determinations is 2.47 per cent. of talc.

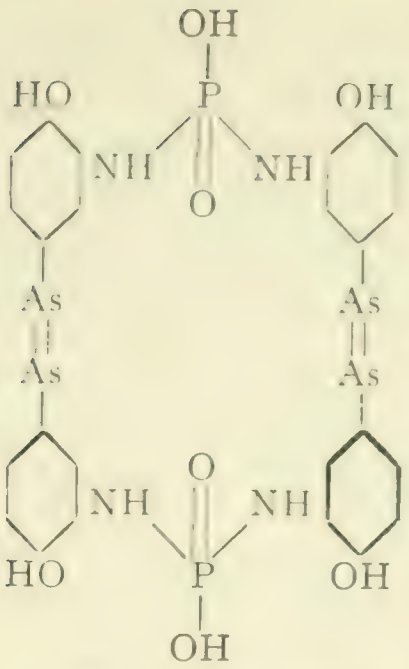
Magnesium Carbonate.—The reserved filtrate and washings from the starch and talc determinations were evaporated to a volume of about 100 c.c., the solution made alkaline with ammonia water and filtered. A trace of residue remained on the filter which, after solution in hydrochloric acid, gave the tests for iron in the ferric state. As the quantity of iron present was small, no attempt was made to determine it quantitatively. The filtrate was treated with an excess of sodium phosphate solution, the precipitate collected, redissolved in dilute hydrochloric acid, reprecitated, collected, dried, heated and weighed as magnesium pyrophosphate in the usual way. The magnesium pyrophosphate from 1.0252 gm. of original material weighed 0.5150 gm., equivalent to 43.82 per cent. of basic magnesium carbonate U. S. P. having the approximate formula $(MgCO_3)_4+Mg(OH)_2+5H_2O$. Another sample of 1.0017 gm. of original material gave 0.4957 gm. of magnesium pyrophosphate, equivalent to 43.16 per cent. of magnesium carbonate U. S. P. A duplicate of 1.0971 gm. of original material (from a different lot of tablets than those used in the first and the second determinations) gave 0.5525 gm. of magnesium pyrophosphate, equivalent to 43.93 per cent. of magnesium carbonate U. S. P. The average is 43.64 per cent. of magnesium carbonate U. S. P.

GALYL

(An abstract appeared in The Journal A. M. A., Nov. 11, 1922, p. 1706)

In 1918, Geo. J. Wallau, Inc., acting as United States distributor for Galyl (manufactured by A. Naline, Garenne, France), requested the Council to consider the product.

At that time, Galyl was stated to be tetrahydroxydiphosphoamino diarsenobenzene, and its molecule was said to be made up of two arsphenamin molecules linked by means of two phosphorous groups (—PO.OH—) in accordance with the following formula:



It was claimed to contain 5.3 per cent. of arsenic and 7.5 per cent. of phosphorus. The product was insoluble in water, and, for use, had to be dissolved by means of a so-called "serum" (a solution of sodium carbonate). Galyl was claimed to be less toxic than arsphenamin, of quicker action on spirilla and of equal therapeutic value.

Later advice was received that the composition of Galyl had been changed. During the course of correspondence it was brought out that only the new Galyl—"Galyl sodium base"—is sold. In the new Galyl the arsenic content was reduced to 18 per cent. In a circular sent to the Council it was stated:

"The newer form of Galyl is a sodium salt of Galyl-base obtained by precipitating a solution of the latter by means of a solution of sodium hydrosulphite. This sodium salt has a formula $C_{24}H_{16}Na_6O_6N_4—P_2As_4.5SO_8Na_2$."

As no tests of a satisfactory nature were furnished, whereby the composition and uniformity of the product might be determined, the A. M. A. Chemical Laboratory was asked to investigate the new Galyl with the idea of devising suitable tests if the product seemed to be what it was claimed to be. (At this time the U. S. Patent Office had issued a patent for the manufacture of old Galyl base; also the U. S. Public Health Service, on the basis of animal experiments, had authorized the importation of the new "Galyl.")

In considering this formula, it would seem that the compound does not possess a definite linkage between the sulphite and arsphenamin groups similar to that of the sulphur group in neoarsphenamin (to which the manufacturers refer as an

example of the relationship of their product). If there is a union, then there are two too many H atoms in the formula. It is likely that the arsenic content is "diluted" to from 18 to 20 per cent. simply by the mechanical incorporation of sodium sulphite. As evidence of the latter point, when Galyl was precipitated out of solution by acetic acid and washed free from sulphurous acid, it did not then respond to the test for sulphur as does neoarsphenamin (see test in N. N. R.)[1]

In working out a suitable test for the phosphorus group, there were evidences that, when solution of the drug Galyl was effected, sodium phosphate was formed. Thus, when a fresh solution of Galyl was treated with magnesia mixture, considerable phosphate was removed (which contained no arsenic), while the arsenic compound and some phosphorus compound remained in the filtrate. The amount of phosphate which would be removed by magnesia mixture progressed as the solution of Galyl stood. From a solution of Galyl, thirty hours old, all of the phosphorus was removed by the addition of magnesia mixture.[2]

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1. Ten cubic centimeters of a solution of Galyl (1: 100) were acidified with acetic acid (odor SO_2 quite pronounced) the precipitate filtered off and washed free from sulphurous acid. The precipitate was transferred to a test tube, hydrochloric acid added, the solution warmed for a few minutes and zinc added. The vapors were tested for hydrogen sulphid with paper moistened with cadmium chlorid—the test was negative; neoarsphenamin responds to the test.

2. A typical experience was as follows: Five cubic centimeters of Galyl solution (1: 100) were tested (within ten minutes of making the solution) at room temperature with ammonium hydroxid solution and magnesia mixture. A precipitate formed immediately; after one hour, the precipitate (A) was filtered off and washed well (Filtrate B). The precipitate (A) contained no arsenic. The filtrate (B) was allowed to stand more than three hours, when another small precipitate formed, and the precipitate removed by filtration—(Filtrate C). The filtrate (C) was evaporated to a small volume (about 4 c.c.) and 4 c.c. of sulphuric acid added; powdered potassium permanganate was then added until oxidation was complete—after cooling and diluting with 10 c.c. of water, hydrogen peroxid solution was added, drop by drop until the manganese oxids were dissolved. After the addition of 3 c.c. of concentrated hydrochloric acid, hydrogen sulphid was passed through rapidly (at 90 C.) until the arsenic was completely precipitated as sulphides. The precipitate was removed by filtration and the filtrate (D) boiled to remove hydrogen sulphid, made ammoniacal and magnesia mixture added—after standing 6 hours, the precipitate was filtered off (precipitate E). (This precipitate may contain some basic manganese sulphid if too much Mn^{++} ion is present). The precipitate (E) was transferred to a test tube with washings and divided in two parts: (1) was treated with nitric acid and ammonium molybdate—some phosphorus was present; (2) was treated with hydrochloric acid and tested for As. No arsenic was present, showing the molybdate test satisfactory. This experiment showed that considerable of the phosphate was removed by the initial magnesia mixture treatment, but *not* all.

When the same solution of Galyl had stood. 30 hours and was then treated with magnesia mixture, practically all of the phosphate was removed by the first precipitation (Ppt. A). Only a trace of phosphate was found in filtrate (B).

When a fresh solution of Galyl was acidified with acetic acid, using methyl red as indicator, phosphorus, in about equal amounts, was found in the filtrate and precipitate, although most of the arsenic was in the precipitate.

The solution of Galyl responds to practically all the tests in N. N. R. for sodium arsphenamin, except that there is present both sulphite (SO_3^{--}) and phosphate (PO_4^{---}) ions. (These tests, however, are mainly those characteristic of the arsphenamin base.) Carbon dioxid does not precipitate the arsphenamin compound when passed through the solution (1:100). This is probably due to the presence of sodium phosphate. It was found that a very small amount of sodium phosphate, added to a solution of sodium arsphenamin, prevents the precipitation of arsphenamin when a vigorous stream of carbon dioxid was passed through the solution. As the manufacturer states, considerable sugar is present.

CONCLUSIONS

The experiments indicate that the sodium salt of diphospho-diarsphenamid ("Galyl sodium base"), if present, is easily hydrolyzed to sodium phosphate and sodium arsphenamin. The manufacturer has presented no proof that a linkage between sodium sulphite and Galyl base exists; on the contrary, the experiments reported herewith disprove any such linkage as occurs in neoarsphenamin (to which the manufacturer refers as a parallel case). When the dry content of the ampule is dissolved in water, either it is partly decomposed into sodium phosphate and sodium arsphenamin, or the original product contains, as such, some sodium arsphenamin and a considerable proportion of free phosphate. In either case, the injection would probably be of a mixture of phospharsenamin (if any is present),[3] sodium arsphenamin, sodium phosphate, sodium sulphite and sugar.

COUNCIL ACTION

In December, 1921, the Council sent the report to the Galyl agent, in duplicate, to facilitate its transmission to the French manufacturers.

In transmitting the report, it was pointed out that if, as the report indicates, (1) Galyl is a mixture containing diphos-

3. From these experiments, Galyl might be considered equivalent to this. The old base of Galyl—diphospho diarsphenamid—is adjusted to from 18 to 20 per cent. of arsenic by the mechanical incorporation of sodium sulphite, which serves both as a preservative and a solvent for the base. About 40 per cent. of sugar is also mixed with these substances to aid in causing more ready solution.

phodiarsphenamid ("old Galyl"), sodium sulphite and sugar, which decomposes in solution yielding sodium arsphenamin, or that (2) Galyl does contain the sodium salt of diphosphodiarsphenamid (mixed with sodium sulphite), which in solution decomposes by hydrolysis into sodium arsphenamin and sodium phosphate, then a radical revision of the advertising claims for Galyl is in order. It was further explained that in such instance the Council might also require evidence that the administration of Galyl possesses advantages over the administration of sodium arsphenamin.

Nothing was received from the agent or the manufacturer to offset the findings of the chemical report.

On the contrary, the work has been essentially confirmed by other investigators, as is evident from the following abstract which appeared in *Chemical Abstracts:*

ARSENOBENZENES

Galyl—Its Formula and Composition.—"The 'Galyl' (A) prepared by M. Naline does not correspond to the chemical formula usually given for A and is not of constant composition, as it is very easily alterable. One sample contained, in addition to the glucose stated on the label, 3 per cent. of sodium chlorid, 12 per cent. of sodium carbonate and 18 per cent. of sodium hydrosulphite. Instead of being neutral as claimed, it was alkaline to both phenolphthalein and litmus. The toxicity of A is of about the same order as that of the other arsenobenzenes investigated by de Myttenaere.[4]

"Galyl" or Tetrahydroxydiphosphamino Diarsenobenzene.—"Two commercial samples of 'Galyl' assayed 18.4 and 22.45 per cent., respectively, of arsenic instead of 35.04 per cent. and 32.9 per cent., which are percentages for the acid compound and the sodium salt, computed on the basis of the published formulas. From these and other published results of a like nature, it is concluded that 'Galyl' is not a definite chemical entity and that each lot manufactured should be assayed for arsenic at the factory and the true percentage stated on the label."[5]

June 20, 1922, Wallau, Inc., advised in reply to an inquiry from the Council, that no reply to the report had been received from the manufacturer, although this had been asked for repeatedly. Wallau stated that this information would

4. De Myttenaere, F.: Bull. Acad. roy. de méd. de Belg. **1**: 249-256, 1921; abstr. in Chem. Abst., Nov. 10, 1921, p. 3724.

5. Dulière, Walter: J. de pharm. **3**: 837, 1921; abstr. Chem. Abstr., March 10, 1922, p. 786.

be sent to the Council when received, and that, pending final action of Galyl by the Council, no new advertising material was being put out but that orders for Galyl were being filled.

The failure of the manufacturer of Galyl to present evidence controverting the findings of the Association's Chemical Laboratory is presumptive evidence that Galyl does not have the composition claimed for it. This conclusion is supported by the evidence of independent investigators.

In the absence of evidence to the contrary, it must be concluded that the composition of Galyl has not been correctly declared (Rule 1) and that the therapeutic claims are unwarranted, since they ascribe to Galyl a composition which it does not appear to possess (Rule 6). Further, since the evidence indicates that the administration of Galyl amounts to the administration of sodium arsphenamin, its use under another name than sodium arsphenamin, and with deceptive claims for its composition, is irrational and a detriment to rational therapy.

Accordingly, the Council declared Galyl inadmissible to New and Nonofficial Remedies.

ADDENDA

In the same issue that was published the abstract of the foregoing report, THE JOURNAL commented editorially.

THE WORK OF THE A. M. A. CHEMICAL LABORATORY

(Editorial reprinted from The Journal A. M. A., Nov. 11, 1922, p. 1690)

When some seventeen years ago the Council on Pharmacy and Chemistry began its work of turning the light on proprietary medicines, its main concern was to let physicians know the composition of many of the proprietary medicines widely advertised in medical journals. At that time the exposure of false or vague and meaningless declarations of identity was considered of basic importance. This fact is shown by the name of the Council and by the appointment of such men as Harvey W. Wiley, then chief of the U. S. Bureau of Chemistry; his associate, Lyman F. Kebler, an authority on drug analysis; Martin I. Wilbert, noted for his work in scientific pharmacy; Samuel P. Sadtler, then professor of chemistry at the Philadelphia College of Pharmacy, and Profs. C. S. N. Hallberg and W. A. Puckner, then teachers at the University of Illinois School of Pharmacy.

This need for work which would bring home to the medical profession the essential secrecy of the drug preparations which they were asked to prescribe led also to the establishment of the A. M. A. Chemical Laboratory under the directorship of Professor Puckner.

The initial report of the Council gave the medical profession the first definite statement of the composition of some of the acetanilid mixtures then so widely exploited as headache remedies. Following this came reports from the Council which gave the results of chemical analyses of such proprietaries as "Tyree's Antiseptic Powder," "Uron," "Thialion," "Sulpholythin," "Labordine," "Campho-Phenique," "Oxychlorin" and "Saliodin." Though many of these preparations were offered to the profession as new chemical discoveries and endowed with imaginary and bizarre chemical formulas, they were, in fact, simple mixtures of well known chemicals, and their analysis presented little difficulty.

As a result of this work of the Council and the laboratory, most promoters of pharmaceutical specialties today know better than to invest money in the exploitation of mixtures the sale of which could be interfered with when once the inevitable happens and the composition of the nostrum is disclosed. But this does not mean that today the composition of all proprietaries is correctly declared. Through ignorance, incompetence or by design, proprietary medicines are still to be found sailing under false colors with regard to their composition. The work of the Chemical Laboratory, however, has become more difficult with these changed conditions. Instead of analyses of mixtures of well known drugs, the laboratory has to do not with the obvious, but with new compounds of novel composition which possess neither the chemical composition nor the constitution ascribed to them. The report of the Council on Pharmacy and Chemistry on "Galyl" that appears in this issue[1] is an example of the more difficult character of work now required of the laboratory.

When "Galyl" was first put on the market, it was claimed to be—and probably was—a compound consisting of two arsphenamin molecules linked together by phosphorus groups. Its administration, however, required manipulations which made its preparation for injection as difficult as that of arsphenamin. With the growing popularity of neo-arsphenamin, the manufacturer of Galyl felt the need of an improved, easily administered preparation. The result was the "new"

1. Galyl: Propaganda for Reform Department, page 1706.

Galyl which is now on the market. This is to be had in solution ready for administration or in the form of a powder which is easily prepared for injection. Fortunately for the profession and the public, if unfortunately for the promoter of Galyl, the A. M. A. Chemical Laboratory investigated this preparation and reached the conclusion that giving this product amounts to the administration of arsphenamin (in the form of the sodium compound) with extraneous inorganic material, and that the "new" Galyl is an unessential and useless duplication of the well established arsphenamin.

Involved and difficult as this work was, it is of the greatest value to our profession, for it obviates the need of comparative clinical trials of Galyl with arsphenamin. The work of the A. M. A. Chemical Laboratory makes it almost certain that Galyl is, for all practical purposes, nothing more than sodium arsphenamin.

BARIUM SULPHATE FOR ROENTGEN-RAY WORK

(An abstract appeared in The Journal A. M. A., Nov. 11, 1922, p. 1687; the full report appeared in The Jour. Am. Pharm. Assn., December, 1922, p. 1072, and also in the Reports of the Council on Pharmacy and Chemistry, 1922, p. 11)

In consideration of the increasing use of barium sulphate in roentgen-ray work, the Council decided to describe barium sulphate for roentgen-ray work in New and Nonofficial Remedies. The description which appears in New and Nonofficial Remedies, 1917, was prepared after consulting interested manufacturers. This description has appeared in subsequent editions of New and Nonofficial Remedies with but minor changes.

A firm which manufactures barium sulphate for roentgen-ray work criticized the test for this substance, which limits the amount of permissible phosphate.

The firm stated that in the manufacture of barium sulphate for roentgen-ray work it has been the aim to supply an article of as high a degree of purity as is commercially obtainable and that the test which it employs to limit the amount of soluble barium salts is more stringent than that prescribed in New and Nonofficial Remedies. The firm stated that, though its product was free from objectionable impurities and equal to that of other brands on the market, it was

confronted with the difficulty that its product, when tested by the New and Nonofficial Remedies standards, appears to contain acid-soluble barium salts. The firm urged that the phosphate test be omitted, in that it shows a noticeable reaction for phosphate when barium phosphate is totally absent, but when nonpoisonous and unobjectionable phosphates, such as calcium phosphate, were present.

The manufacturer submitted the tests which were used for the control of barium sulphate for roentgen-ray work. These included the test for soluble barium salts and also the following test for the fineness (fluffiness) of the product:

> Introduce 15 gm. of the material into a 50 cubic centimeter glass-stoppered cylinder and add sufficient water, so that, after thoroughly agitating the mixture, it has a total volume of 50 c.c. After this mixture has stood for ten minutes, the upper or aqueous layer should not exceed 5 c.c.

The objection to the phosphate test appeared well founded, and the proposed revision of the text for soluble barium salts and the "fluffiness" test worthy of consideration; therefore, the A. M. A. Chemical Laboratory drew up a tentative revision of the N. N. R. standards which omitted the phosphate test and included the more sensitive barium test and the "fluffiness" test. It submitted this revision to those firms whose brands of barium sulphate for roentgen-ray work had been admitted to New and Nonofficial Remedies.

In general, the replies which were received indicated that the firms were ready to accept the more stringent test for barium salts, other than barium sulphate, and also the "fluffiness" test. One firm, however, definitely objected to the latter test on the ground that users of barium sulphate in roentgen-ray laboratories had found difficulty in preparing suspensions with a too "fluffy" product. Some of the firms did not favor omission of the phosphate test on the ground that appreciable amounts of insoluble phosphate, such as calcium phosphate, should not be permitted in barium sulphate, and two firms recommended the adoption of a test limiting the water and acid soluble material in barium sulphate. For the latter test, the argument was advanced that, under the present N. N. R. standards, large quantities of foreign salts are permitted.

Since one firm held that a "fluffy" barium sulphate had proved unsatisfactory, inquiry was made of a representative group of roentgenologists as to whether they considered it desirable that barium sulphate be required to be in a finely divided physical condition. Inquiry was also made as to the brands which had been found satisfactory.

In general, the twenty-eight replies which were received held that barium sulphate should be in as fine a state of subdivision as possible. However, many of the replies held that extreme fineness was not essential. This was emphasized by the enumeration of the brands that had been used with satisfaction. One correspondent stated that a medium fineness was to be preferred and that difficulty had been experienced in the use of a very fine powder. Another correspondent stated that a powder passing a forty mesh sieve was satisfactory, and another that a product was acceptable so long as it did not clog up an enema tube (containing no particles larger than a grain of wheat). Several objected to the high price charged for some of the very finely divided products. The following is the reply of a prominent roentgenologist:

> We have used barium sulphate from various manufacturers, and have found little difference, except as to price. For example, some manufacturers label their barium sulphate, "Specially prepared for x-ray purposes," and boost the price three or four hundred per cent. For the last ten years we have used ————————'s chemically pure barium sulphate. It has always proved entirely satisfactory. Other things being equal, I think that perhaps the barium sulphate which remains longest in suspension would be most desirable. To sum up, I would answer your first question by saying that it is not essential for the barium sulphate to be any more finely divided than it is in the various brands that we have used. Second, all brands were found to be satisfactory.

From the replies of the users of barium sulphate, it appears that the fluffiness test is not essential. It has the objection that a powder containing a small proportion of very fine material will respond favorably to the test, even though it contains a relatively large proportion of coarse particles.

The replies also make it clear that the phosphate test (which makes a product containing a negligible amount of calcium phosphate inadmissible) is unnecessary. The adoption, in its place, of a test which shall require reasonable freedom from foreign salts, along with tests which shall guarantee freedom from water soluble and acid soluble barium salts and freedom from heavy metallic salts, such as those of lead, would appear adequately to insure a barium sulphate for roentgen-ray work which is of acceptable quality and which can be produced at a reasonable price.

The revised tests and standards for barium sulphate which were drawn up on the basis of the available evidence were submitted for criticism to the firms whose brands of barium sulphate for roentgen-ray work stand admitted to N. N. R. In consideration of the replies received, the laboratory recommends the adoption of the following tests and standards for

barium sulphate for roentgen-ray work, in place of those now in New and Nonofficial Remedies:

BARIUM SULPHATE FOR ROENTGEN-RAY WORK.—**Barii Sulphas Roentgenographicus.**—Barium sulphate freed from soluble barium salts.

Barium sulphate for roentgen-ray work is a fine white odorless, tasteless and relatively light powder, free from grittiness, and is insoluble in water and organic solvents as well as in aqueous solutions of acids and of alkalies.

Mix 0.5 Gm. of barium sulphate for roentgen-ray work with 2 Gm. each of anhydrous sodium carbonate and anhydrous potassium carbonate; heat the mixture in a crucible until fusion is complete; treat the resulting fused mass with hot water, and then filter. Acidify a portion of the filtrate with hydrochloric acid; add 1 Cc. of barium chloride solution; a white precipitate forms (*sulphate*). Dissolve a portion of the well washed residue in acetic acid and add 1 Cc. of potassium chromate solution; a yellow precipitate forms (*barium*). Dissolve another portion of the well-washed residue in a small amount of hydrochloric acid; place a drop of the solution on the loop of a clean platinum wire, and ignite in a nonluminous flame; a green color is imparted to the flame (*barium*).

Boil 10 Gm. of barium sulphate for roentgen-ray work with 100 Cc. of hydrochloric acid, 1 per cent., for ten minutes, and add sufficient water to restore the original volume. Cool the mixture and filter through a paper which has been washed previously with the diluted hydrochloric acid, returning the first portions if necessary until a perfectly clear filtrate is obtained. Evaporate 50 Cc. of the filtrate to dryness on the water bath; add 2 drops of hydrochloric acid, U. S.P., and 10 Cc. of hot water; filter through a hydrochloric acid washed filter; wash with 5-10 Cc. of hot water, and evaporate the filtrate to dryness in a tared dish on the water bath. The residue, when dried to constant weight at from 100 to 110 C. should not be more than 0.3 per cent. (*limit of water and dilute acid soluble nonvolatile material*). Treat the residue with 10 Cc. of water; filter the solution through a hydrochloric acid washed filter and add 0.5 Cc. of diluted sulphuric acid to the filtrate; no turbidity should develop within one-half hour (*soluble barium salts*).

Boil 5 Gm. of barium sulphate for roentgen-ray work with 50 Cc. of diluted acetic acid. Filter while hot and saturate the clear filtrate with hydrogen sulphide; no turbidity or coloration should be formed (*heavy metals*).

Triturate 2 Gm. of barium sulphate for roentgen-ray work with 5 Cc. of concentrated hydrochloric acid, then add 10 Cc. of a freshly made, saturated solution of stannous chloride; no dark coloration occurs within one-half hour (*arsenic*).

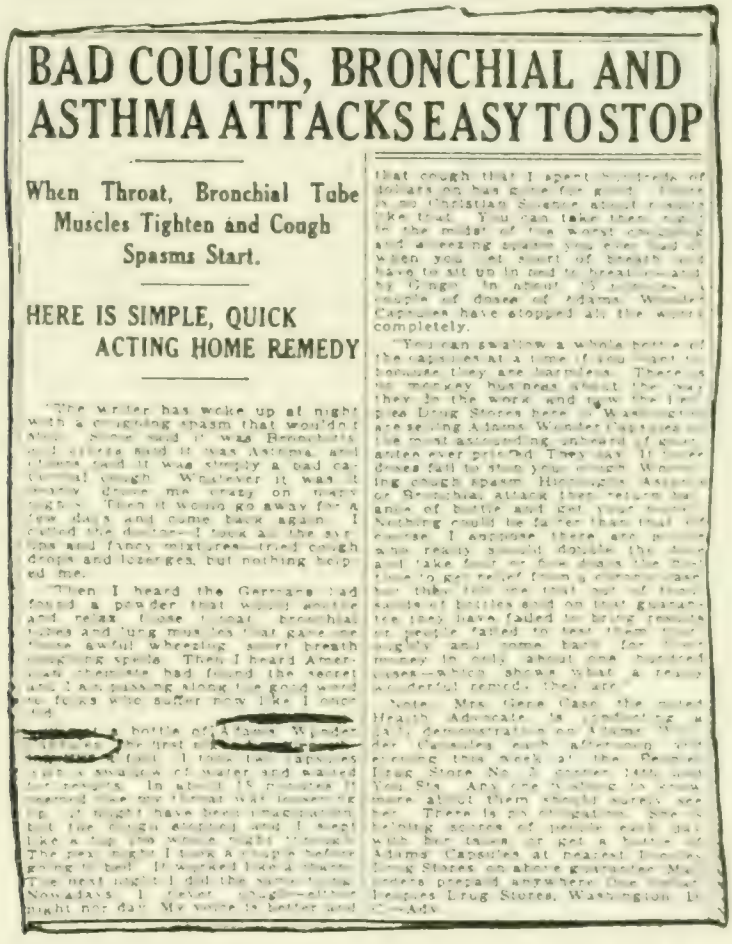
The Council adopted the report of the American Medical Association Chemical Laboratory on Barium Sulphate for Roentgen-Ray Work and accordingly directed that the revised tests and standards be included in New and Nonofficial Remedies, 1923.

ADAMS' WONDER CAPSULES

The Earle Chemical Company Brings Benzyl Succinate Into the "Patent Medicine" Field

(Abstracted, with additions, from The Journal A. M. A., Nov. 25, 1922, p. 1867.)

"Adams' Wonder Capsules" are sold, although, apparently, not made, by the Earle Chemical Company, Inc., of Wheeling, W. Va. This same concern puts out a line of "patent medi-



BAD COUGHS, BRONCHIAL AND ASTHMA ATTACKS EASY TO STOP

When Throat, Bronchial Tube Muscles Tighten and Cough Spasms Start.

HERE IS SIMPLE, QUICK ACTING HOME REMEDY

Typical newspaper advertisement (reduced) of Adams' Wonder Capsules.

cines": "Hypo-Cod," "Gray-Tabs" and "Phos-Pho Vitamine."

In some of the newspaper advertisements of Adams' Wonder Capsules, women and girls are urged to call at some local drug store and "talk about their ailments with a kindly, motherly woman of the experience and sympathetic understanding of Mrs. Gene Case, the noted Health Advocate." The public is told, further, that "Mrs. Case has been giving free treatments daily" and those who call on her are in no way "obligated or importuned constantly to try some expen-

sive long weary treatment." This "noted Health Advocate," it appears, recommends "Adams' Wonder Capsules" for girls and women "who are troubled with Periodical pains, cramps and headache at Menstrual time, or who have Neuritis, Neuralgia, Stomach, bowel or bladder pains. . . ."

A specimen of "Adams' Wonder Capsules" was examined and the following report published in THE JOURNAL:

"The package of Adams' Wonder Capsules contained twenty capsules, the average weight of each capsule being about 5.1 grains. No information is furnished by the manufacturer concerning the composition but the statement is made that the product is 'A Wonderful New Discovery . . . discovered by chemists in Germany during the War.'" The capsules contained a coarsely granular, white, odorless powder which, under the microscope, was seen to be in the form of hexagonal rhombohedra, although many of the crystals were broken and irregular in shape. The material was compared with known specimens of benzyl succinate; the two were seen to have the same crystalline structure.

"The powdered and dried crystals melted at 43 C., the same temperature at which a specimen of known benzyl succinate melted. The crystals also responded to other tests for this substance. As a result of the examination, it was concluded that Adams' Wonder Capsules are simply capsules of benzyl succinate."

THE JOURNAL commented on Adams' Wonder Capsules as follows:

"Incidentally, it is of interest to note that the claim made by the exploiters of this preparation that Adams' Wonder Capsules were 'discovered by chemists in Germany during the War' is untrue. Benzyl succinate was first prepared by Italian chemists over forty years ago (Zanna and Guareschi, *Gazz. chim. ital.* **17**:256, 1881), but its therapeutic properties were discovered by American pharmacologists about 1920."

Details of Analysis

Alkaloids.—Some of the material was shaken with water containing a trace of hydrochloric acid and the mixture filtered. The filtrate did not respond to the usual tests for alkaloids.

Acetyl Salicylic Acid.—To a portion of the above described filtrate a trace of ferric chlorid solution was added. No violet color was produced.

Acetanilid.—The absence of acetanilid was shown by the negative result obtained with the phenylisocyanid test.

Amidopyrin.—Some of the material was shaken with water and the mixture filtered. The filtrate gave no color on the addition of a trace of ferric chlorid solution.

Benzyl succinate.—To a mixture of 1 c.c. of diluted sulphuric acid and 10 c.c. of tenth-normal potassium permanganate about 0.1 gm. of the substance was added and the mixture warmed. The odor of benzaldehyd became noticeable.

About 2 gm. of the material were boiled with 30 c.c. of half-normal alcoholic sodium hydroxid in a reflux apparatus for 1 hour, the mixture cooled, filtered and the precipitate washed with alcohol. The precipitate was dissolved in the minimum quantity of warm water, and the solution acidified with concentrated hydrochloric acid. The precipitate was recrystallized once from a few c.c. of hot water. The crystals melted at 182 C. To the alcoholic filtrate 25 c.c. of water were added and the solution boiled until the alcohol was removed. The alkaline solution was shaken twice each with 10 c.c. of ether and the solvent evaporated. The residue had the odor of benzyl alcohol.

PART III

REPORTS NOT PREVIOUSLY PUBLISHED

ANALYSIS OF SOME DOLOMOL COMPOUNDS

The following Dolomol Compounds, manufactured by Brewer and Co. Inc., were analyzed by the Laboratory at the request of the Council on Pharmacy and Chemistry:

Dolomol-Iodin

Dolomol-Iodin is claimed to contain 5 per cent. of iodin "in a free and active state." Analysis showed the product to contain less than 0.1 per cent. of free iodin. This would be expected when it is remembered that the Dolomol base is "a stearo-palmitate of magnesium" which would react with iodin. The product therefore does not comply with the label.

Dolomol-Acid Boric

Dolomol-Acid Boric is claimed to contain 20 per cent. of boric acid. Analysis shows the product to contain 20.7 per cent. of boric acid. This agrees with the claimed amount.

Dolomol-Calomel

Dolomol-Calomel is claimed to contain 25 per cent. of calomel. Several years ago the product was found misbranded by the government. The former manufacturers explained that the calomel, due to greater density, had "settled out" of a batch, causing the packages to contain varying amounts. In view of the foregoing, Dolomol-Calomel was analyzed. It contained mercury equivalent to 24.5 per cent. of mercurous chlorid (calomel) which agrees fairly closely with the claimed amount.

Details of Analysis

Iodin in Dolomol-Iodin 5 Per Cent.—A sample weighing 3.9582 gm. was shaken thoroughly with chloroform and the chloroform filtered. The chloroform extract (color which showed only a very small amount of iodin) was transferred to an erlenmeyer flask and water added. Tenth-normal sodium thiosulphate was added until color of chloroform disappeared after shaking. The amount of sodium thiosulphate consumed was 0.2 c.c., equivalent to 0.07 per cent. of iodin.

Boric Acid in Dolomol-Boric Acid 20 Per Cent.—A weighed sample was placed in a separatory funnel, water, diluted sulphuric acid and ligroin added; the mixture was shaken well, and the aqueous layer drawn off. The ligroin layer was washed with 2 portions of water and the aqueous solutions combined. The boric acid extract was then made exactly neutral to methyl red, 33 per cent. of glycerin by volume added and titrated with normal sodium hydroxid using phenolphthalein as indicator: (*a*) 2.0379 gm. required 7.0 c.c. of normal sodium hydroxid, equivalent to 21.0 per cent. of boric acid; (*b*) 1.4595 gm. required 4.8 c.c. of normal sodium hydroxid, equivalent to 20.4 per cent. of boric acid.

Mercurous Chlorid in Dolomol-Calomel 25 Per Cent.—The weighed sample was placed in a 150 c.c. beaker and moistened with 5.8 c.c. of alcohol. Fifteen c.c. of water, 15 c.c. of bromin water and 2.4 c.c. of diluted nitric acid were added and the solution heated to boiling on an electric hot plate; several 5 c.c. portions of bromin water were added. This oxidized mercurous chlorid to the mercuric form. An oily substance floated on top. The liquid was filtered through a *hot* filter and washed with boiling water. The filtrate was electrolized with a current of 2.5 amperes and 8-9 volts. The mercury was washed, dried and weighed in the manner described under potassium mercuric iodid, Annual Reports A. M. A. Chemical Laboratory, 1921, Vol. 14, p. 59. (*a*) A sample weighing 1.9343 gm. yielded 0.4016 gm. mercury, equivalent to 24.42 per cent. of mercurous chlorid—"calomel"; (*b*) 1.7390 gm. yielded 0.3632 gm. mercury, equivalent to 24.56 per cent. of cercurous chlorid.

NOTES ON QUINIDIN AND QUINIDIN SULPHATE

L. E. Warren, Ph.C., B.S.

Quinidin is a stereoisomer of quinin which occurs in small quantities in various species of *Cinchona*, particularly in *Cinchona amygdalifolia*, *C. calisaya*, *C. ovata*, *C. pitayensis* and *C. succirubra*. In working cinchona barks for alkaloids, quinidin is usually obtained from the mother liquor after most of the quinin sulphate has crystallized out. In the cultivation of cinchona in Java it is said that some strains have been developed in which nearly all of the quinidin has been eliminated. For many years quinidin has been used in medi-

cine as a substitute for quinin although its antimalarial efficiency is believed to be slightly less than that of quinin.[1] The quinidin of commerce is nearly always contaminated with hydroquinidin. It is exceedingly difficult to separate quinidin from hydroquinidin, but since the therapeutic properties of the two alkaloids are believed to be practically identical,[2] the presence of this impurity in quinidin is not a serious matter from the therapeutic viewpoint. In the earlier days, quinidin, being a by-product in the manufacture of quinin, was considerably cheaper than the other alkaloid; but of late years, the prices of the two alkaloids have not been markedly different, quinin usually being a little cheaper. Owing to the fact that quinidin may be prepared in much larger crystals than quinin, the former has often been preferred in pharmacy for the preparation of suspensions in syrups, particularly if flavored with chocolate, such preparations being relatively free from bitter taste and suitable for administration to children. A syrup of quinidin is described in the National Formulary IV.

According to Hamburger[3] quinin has been used as a heart sedative for a good many years in addition to its use as an antimalarial and antipyretic, but it was not until 1918[4] that quinidin was found to be less toxic and more effective for this purpose than quinin. Since then, quinidin has been attracting considerable attention in the treatment of auricular fibrillation, the normal heart rhythm being said to be restored in a certain number of cases. Its use for this purpose is still in the experimental stage. The use of quinidin is not without danger;[5] syncope, apnea, pulselessness,[3] embolism[6] and even death[7] have been reported following its administration.

In view of the considerable use of quinidin and its salts in therapy, it seemed desirable that one or more of these be standardized by admission to New and Nonofficial Remedies. Quinidin alkaloid is described in the National Formulary, but since quinidin is most often prescribed as the sulphate, it appeared natural that this salt should be selected particularly for standardization.

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1. MacGilchrist: Ind. J. Med. Res. **9**: 1, 1915.
2. Lewis, Drury, Iliescu and Wadd: Heart **9**: 55, 1921.
3. Hamburger: Ibid. **77**: 1797, 1921.
4. Frey: Berl. klin. Wchnschr., 1918.
5. Hewlett and Sweeny: J. A. M. A. **77**: 1793, 1921.
6. McKenzie and Orr: Brit. Med. Jour. **2**: 576, 1921.
7. Sappington: J. A. M. A. **78**: 59, 1922.

Accordingly, specimens of quinidin and of quinidin sulphate were obtained and were subjected to examination. One specimen each of quinidin and of quinidin sulphate of the Mallinckrodt Chemical Works brand, two specimens of quinidin alkaloid and one of quinidin sulphate each from the Powers-Weightman-Rosengarten Co. and from the New York Quinine and Chemical Works were studied.

Examination of Quinidin

With one exception each specimen of quinidin studied was a coarsely granular, crystalline, white powder. The one exception (a specimen of the N. Y. Q. brand) was in the form of fine, amorphous, white powder.

Quinidin is described in the literature either as not containing any water of hydration or as containing 1½ molecules. Tests on the specimens showed about 10 per cent. of loss on drying at 100 C., except in one specimen (amorphous powder) which lost about 2.3 per cent. Theory for two molecules of water of hydration requires 10.00 per cent. of water of hydration.

The findings for the several specimens were as follows: M. C. W. 10.83 per cent.; P. W. R. (A) 9.72 per cent., (B) 10.79 per cent; N. Y. Q. (A) 10.54 per cent., (B) 2.30 per cent. On exposure to dry air the crystalline specimens lost a small amount in weight, thus indicating that crystallized quinidin is slightly efflorescent. Each of the specimens was essentially free from ash. Each of the specimens conformed to the N. F. test for foreign cinchona bases. This test depends on the relative insolubility of quinidin iodid at 15 C. as compared with the solubilities of the iodids of the other cinchona bases. The test is given herewith as applied to the alkaloid. In testing the neutral salts, it is, of course, unnecessary to add diluted sulphuric acid.

Dissolve 0.5 gm. of quinidin in 15 c.c. of boiling distilled water, with just enough diluted sulphuric acid to form a solution neutral to litmus paper, and add 5 c.c of potassium iodid solution. Agitate the mixture slightly, cool it to 15 C. and keep it at this temperature for one hour with occasional stirring. A white precipitate is formed (*difference from quinin*). Filter out the precipitate and add 2 drops of ammonia water to the filtrate; not more than a slight turbidity results (*limit of other cinchona alkaloids*). Care must be taken to have the liquid perfectly neutral before the addition of the potassium iodid solution; if slightly acid, very dilute ammonia water must be added, drop by drop with constant stirring until the solution becomes exactly neutral to litmus paper.

The test, as above described, was applied to each of the specimens of quinidin under examination and each complied with the requirements of the test.

Each of the specimens after drying at 100 C. melted between 169 and 170 C.

The examination indicated that each of the specimens was of good quality.

Based partly upon the results obtained in the examination and partly upon the literature, the following tentative description for quinidin was prepared:

QUINIDIN.—Quinidina.—An alkaloid, $C_{20}H_{24}O_2N_2+2H_2O$, obtained from the bark of various species of *Cinchona*.

Quinidin occurs in white crystals or as an amorphous, white powder; odorless; taste intensely bitter and persistent; efflorescent in dry air.

Quinidin is very slightly soluble in water; soluble in alcohol and ether; freely soluble in chloroform; very slightly soluble in petroleum benzin.

The aqueous solution of quinidin is alkaline to litmus and its alcoholic solution is dextrorotatory. A solution of quinidin in diluted sulphuric acid (1: 1,000) shows a strong blue fluorescence.

Quinidin loses its water of hydration at 100 C. The dried alkaloid melts at about 168 C.

Add a few drops of bromin water to 10 c.c. of an aqueous solution of quinidin (1: 1,000), prepared with just sufficient diluted sulphuric acid to produce complete solution, and follow with ammonia water in slight excess. The liquid acquires an emerald-green color.

Dissolve about 0.1 gm. of quinidin in 15 c.c. of hot water containing a few drops of diluted sulphuric acid; cool the solution; add 1 c.c. of silver nitrate solution and stir the mixture with a glass rod. A white, crystalline precipitate forms after a short interval (*distinction from many other alkaloids*).

Dissolve about 0.1 gm. of quinidin in 10 c.c. of warm water, containing a slight excess of diluted hydrochloric acid; add an excess of potassium iodid solution and agitate. An orange yellow, crystalline precipitate forms after an interval (*distinction from quinin*).

Dissolve 0.5 gm. of quinidin in 15 c.c. of boiling distilled water, with just enough sulphuric acid to form a solution neutral to litmus paper, and add 5 c.c. of potassium iodid solution. Agitate the mixture gently; cool it to 15 C., and keep it at this temperature for one hour, with occasional stirring. A white precipitate is formed (*difference from quinin*). Filter out the precipitate and add 2 drops of ammonia water to the filtrate; not more than a slight turbidity results (*limit of other cinchona alkaloids*). Care must be taken to have the liquid perfectly neutral before the addition of the potassium iodid solution; if slightly acid, very dilute ammonia water must be added, drop by drop, with constant stirring until exact neutrality to litmus is attained.

A solution of about 0.1 gm. of quinidin in 5 c.c. of sulphuric acid is not darker than pale yellow (*organic impurities*).

Incinerate about 1 gm. of quinidin, accurately weighed. The ash does not exceed 0.1 per cent.

Dry about 1 gm. of quinidin, accurately weighed, to constant weight at 100 C. The loss does not exceed 11 per cent.

Quinidin Sulphate

A specimen each of quinidin sulphate was examined from each of the following brands:

Mallinckrodt Chemical Works.

Powers-Weightman-Rosengarten Company.

New York Quinine and Chemical Works.

Each of the specimens was a white, coarsely granular, crystalline powder. Each lost weight when dried at 100 C., but the dried salt regained most of the loss when exposed to the air for a few days.

Water of hydration was determined by drying at 100 C. in an air bath. The losses were: M. C. W. 4.53 per cent.; P. W. R. 4.57 per cent.; N. Y. Q. 4.54 per cent. Theory for one molecule of water of hydration requires 4.63 per cent.

Each specimen dissolved in water without appreciable residue and none gave any appreciable residue on burning. The specimens were each found to be of good quality. Tentative tests and standards were prepared for quinidin sulphate analogous to those prepared for quinidin. These are as follows:

QUINIDIN SULPHATE.—Quinidinae Sulphas. $-(C_{20}H_{24}O_2N_2)_2.H_2SO_4+2H_2O$.—The sulphate of quinidin.

Quinidin sulphate occurs as minute, silky, white crystals, usually cohering in tufted masses; odorless; taste very bitter and persistent; permanent in the air. On exposure to light, it acquires a brownish tint.

Quinidin sulphate is soluble in water, alcohol and chloroform; very slightly soluble in ether.

The saturated aqueous solution of quinidin sulphate is faintly alkaline to litmus and is dextrorotatory..

Dissolve about 0.01 gm. of quinidin sulphate in 10 c.c. of water; add a few drops of bromin water to the solution, and follow with ammonia water in slight excess. The liquid acquires an emerald-green color.

The aqueous solution gives a white precipitate with barium chlorid solution which is insoluble in hydrochloric acid.

Quinidin sulphate loses its water of hydration (4.63 per cent.) at 100 C.; but the dried salt reabsorbs it on exposure to moist air.

To about 5 c.c. of a saturated, aqueous solution of quinidin sulphate, add 1 c.c. of silver nitrate solution and stir the mixture with a glass rod. A white, crystalline precipitate forms after a short interval (*distinction from the salts of many other alkaloids*).

Dissolve 0.5 gm. of quinidin sulphate in 15 c.c. of boiling water and add 5 c.c. of potassium iodid solution; agitate the mixture slightly; cool it to 15 C., and keep it at this temperature for one hour, with occasional stirring. A white precipitate is formed (*difference from quinin*). Filter out the precipitate and add 2 drops of ammonia water to the filtrate; not more than a slight turbidity results (*limit of other cinchona alkaloids*).

A solution of about 0.1 gm. of quinidin sulphate in 5 c.c. of sulphuric acid is not darker than pale yellow (*organic impurities*).

Incinerate about 0.5 gm. of quinidin sulphate, accurately weighed; the ash does not exceed 0.1 per cent.

Dry about 1 gm. of quinidin sulphate, accurately weighed, to constant weight at 100 C.; the loss does not exceed 5 per cent.

The chemical reactions of quinidin salts are tabulated herewith: Part of the information given in Table I has been obtained from the literature, but a part of it has been collected as a result of tests carried out in these studies. From the tabulation it will be noted that the most characteristic tests for quinidin as compared with the other common cinchona bases are the precipitates produced with potassium iodid, silver nitrate, chromic acid, potassium ferrocyanid and potassium sulphocyanate solutions. None of these salts is sufficiently insoluble to be of much use in the quantitative separation of quinidin from quinin or from the other cinchona bases.

TABLE I.—*Reactions of Some of the Cinchona Bases*

Reagent or Test	Cinchonidin Sulphate	Cinchonin Sulphate	Quinidin Sulphate	Quinin Sulphate
Potassium iodid	0	0	White	0
Silver nitrate	0	0	White cryst	0
Chromic acid	0	0	Orange	0
Potassium ferrocyanid	0	0	Pale yellow cryst	0
Potassium sulphocyanate	0	0	White cryst	0
Sodium nitroprusside	0	0	White cryst	White cryst
Sodium salicylate	White voluminous cryst	White sparing	White sparing	White voluminous cryst
Mercuric chlorid	White	White	White	White
Sodium bicarbonate	0	White (sparing)	0	0
Gold chlorid	Lemon-yellow	Lemon-yellow	Lemon-yellow	Lemon-yellow
Palladium chlorid	Brownish-gray	Brownish-gray	Brownish-gray	Brownish-gray
Platinum chlorid	Pale salmon	Pale yellow	Pale salmon	Pale yellow
Potassium chromate	Yellow sparing	Yellow cryst	Yellow cryst	Redissolves
Potassium sodium tartrate	White cryst	0	0	Sparing white
Bromin water (in excess)	Orange-Yellow	Orange-Yellow	Orange-Yellow	Orange-Yellow
Ammonium oxalate	White slow to form (sparing)	0	0	White cryst
Picric acid	Yellow	Yellow	Yellow	Yellow
Thalleioquin	0	0	Positive	Positive
Optical rotation	--	+	+	—

NOTES ON THEOCIN

A specimen of Theocin was examined with the view of its admission to New and Nonofficial Remedies as a proprietary brand of theophyllin now official in the U. S. Pharmacopeia. Accordingly the U. S. P. tests for theophyllin were applied to the specimen.

The Pharmacopeia states that theophyllin is soluble in 100 parts of water (at 25 C.). It was noted that if a solution of 1 gm. of theocin in 100 c.c. of warm water were allowed to cool, crystals of theocin separated on standing. This indicated that theocin required more than 100 parts of water for solution at 25 C. Accordingly the following test was made:

To 5.0088 gm. of theocin about 250 c.c. of warm water were added. After solution took place, the liquid was poured through a cotton filter into a 500 c.c. flask, and the filtrate made up to 500 c.c. Then 1 c.c. more of water was added, the solution mixed thoroughly and allowed to stand for ten days at room temperature with occasional agitation. At the expiration of this time, some of the solution was passed through a filter, a weighed portion of the filtrate evaporated, the residue dried at 100 C. and weighed. From 27.6120 gm. of the filtrate, a residue of 0.2088 gm. was obtained. This is equivalent to 0.2259 gm. of the hydrated substance. Subtracting 0.2259 gm. from 27.6120 gm. gives 27.3861 gm. of water in the solution taken. Since 0.2259 gm. of theocin requires 27.3861 gm. of water for solution, 1 part of theocin requires $\frac{0.2259}{27.3861} = 121.23$ parts of water for solution at 23 C.

OTITA

During the latter months of 1921 physicians received a circular letter on the stationery of Clarke W. Mangun, M.S., M.D., Iowa Falls, Iowa, notifying them that Dr. Mangun had "for several years been studying and experimenting on the medical treatment of chronic otitis media," and that as a result of his study he had "devised a treatment which has been unusually successful." Physicians who wished to use this product could obtain "directions and sufficient medicine

for four ordinary chronic cases" for the sum of $5.00. Nothing was said in the circular letter regarding the character of this new discovery. A month later a "follow-up" letter came, in which the physician was told:

"The specific medicine employed is manufactured under my personal supervision so as to assure its purity and therapeutic activity. It is being marketed under the trade designation of 'Otita.'"

While this letter further extolled the virtues of Otita, declaring that the "preparation stands alone in a field of difficult therapeutics," no information was given regarding the composition of this preparation which the doctors were asked to administer to their patients. Dr. Mangun claimed that:

"Otita is possessed of analgesic and antiseptic properties without astringency, is cleansing in character, allays inflammation and promptly reduces the discharge."

Physicians who made inquiries of Dr. Mangun concerning the composition of Otita received evasive or noninformative replies. So many inquiries were received by THE JOURNAL that it was deemed worth while to examine the product. A $5.00 bottle of Otita was procured and subjected to chemical examination.

The specimen of Otita examined was a clear, colorless, somewhat viscous liquid having a bitter-sweet taste and an acid reaction to litmus. The package contained about 1 fluid-ounce. The specific gravity of the preparation was 1.1355 at $\frac{25\text{ C.}}{25\text{ C.}}$. Glycerin, an alkaloid and a chlorid were present; the two last in small amounts. Other medicaments were absent or present only in traces. The alkaloid amounted to about 0.336 gm. per 100 c.c., equivalent to about 1½ grains to each fluid-ounce. The alkaloid appeared to be quinin, or a substance closely related to quinin but owing to the small quantity present it was not possible positively to identify it. The quantitative relationship between the total chlorid present and the total alkaloid indicated the probability that the medicament is quinin dihydrochlorid. Glycerin comprised about 50 per cent. by weight of the preparation. From the results of the examination it seems probable that Otita is a solution of about 1.8 grains of quinin dihydrochlorid per fluid-ounce in a mixture of equal volumes of glycerin and water.

Details of Analysis

Specific Gravity.—The specific gravity of the preparation was determined with a pycknometer. It was found to be 1.1355 at $\frac{25\text{ C.}}{25\text{ C.}}$

Total Alkaloid.—The material used for the specific gravity determination was diluted with water, made alkaline with ammonia water and repeatedly extracted with ether until extraction was complete. The solvent was washed with water, evaporated on the steam bath, the residue dried at 100 C. and weighed. From 28.3537 gm. of material an alkaloidal residue weighing 0.0838 gm. was obtained equivalent to 0.3356 gm. of alkaloid per 100 c.c. This is equivalent to 0.4111 gm. of quinin dihydrochlorid per 100 c.c., or about 1.8 grains per fluid-ounce.

Chlorid.—The material in the separator from which the alkaloid had been removed was evaporated to half its volume to remove ether and free ammonia and the residue diluted to 250 c.c. Portions of this solution were used for the determination of chlorid by the silver chlorid precipitation method in the usual way. Aliquot portions of 100 c.c. gave 0.0252 gm. and 0.0265 gm. of silver chlorid, equivalent to 0.259 gm. of silver chlorid per 100 c.c. of original material, or 0.3587 gm. of quinin dihydrochlorid.

Glycerol.—This was estimated approximately by the specific gravity of the mixture, the small quantity of quinin salt not being considered. As previously stated the specific gravity of the mixture at $\frac{25\text{ C.}}{25\text{ C.}}$ was 1.1355. According to Nicol's computations[1] (which were made at 20 C.) this is equivalent to about 52.63 per cent. of absolute glycerol. The error due to the difference in the temperature at which the specific gravity of the substance was taken and at which Nicol's computations were made was discounted since an approximation was considered sufficient.

SULFARSENOL

Charles Leich and Company submitted for consideration by the Council on Pharmacy and Chemistry an arsphenamin derivative, "Sulfarsenol." It was claimed to be "Sodium Salt of the Acid Sulphurous Ether of Monomethylol amino arseno-

1. Nicol: Pharm. Jour. [3] **18**: 302, 1887.

phenol" group. The product is manufactured by Laboratoire de Biochimie Medicale, Paris, France.

The Chemical Laboratory's aid was asked by the Council's referee; the laboratory suggested that Charles Leich and Company offer explanation of the following:

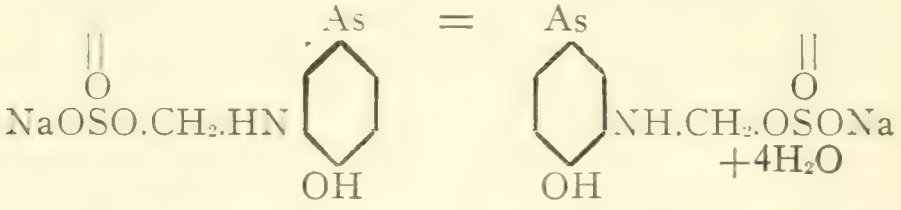
1. In some formulas both amino groups of arsphenamin base have been condensed with the "sodium acid sulphurous, methylol ether" group; in other formulas only one amino group has been attached.

2. Sufficient chemical evidence has not been presented to show that the product differs essentially from neoarsphenamin. No test has been given to show that the sulphur has a valence of 4 in Sulfarsenol, whereas the valence in neoarsphenamin is 2, the former having an extra molecule of oxygen attached to the sulphur.

3. Sulfarsenol was examined chemically in Europe last year by F. de Myttenaere with Magnus and Van Boeckel. They found, according to *Chemical Abstracts* (June 20, 1921, p. 1963) that Sulfarsenol "varied irregularly, indicating more or less of the mono-substituted derivative," and that the amount of the easily "mineralizable" arsenic also varied.

In reply they submitted a brief from the French makers of Sulfarsenol.

1. In this brief the formula was stated to be:



Charles Leich and Company stated further that this formula would be used in all the English literature. The French consultants claimed that the mono-substituted formula or product has not been employed since 1918.

In view of the reply, the laboratory was of the opinion that objection to the discrepancy had been met, particularly in light of the unsatisfactory chemical definition of neoarsphenamin.

2. Through Charles Leich and Company a number of tests were submitted to distinguish Sulfarsenol from "neoarsphenamin." These were tried on Sulfarsenol, Neoarsphenamin-Metz (1919 specimen) and neoarsphenamin-D. R. I. (1919 specimen) using a 1 per cent. solution. Although there were certain differences between Sulfarsenol and Neoarsphenamin-

Metz yet these chemical differences were relatively no greater than between Neoarsphenamin-Metz and Neoarsphenamin-D. R. L. In fact, Neoarsphenamin-D. R. L. was at times more similar in reaction to Sulfarsenol than to Neoarsphenamin-Metz. One outstanding difference was that Sulfarsenol solution (1 per cent.) was acid to litmus while the same strength Neoarsphenamin solutions were neutral. It seemed therefore that in many instances the so-called distinguishing tests were different simply due to different hydrogen ion concentrations prevailing. Then also the so-called inert salt content also may affect the various tests.

The Laboratory's opinion, as expressed to the Council was that Sulfarsenol is an arsphenamin derivative closely resembling Neoarsphenamin. The exact chemical constitution could not be proved without considerable research, time for which was not available; however, Sulfarsenol is on as sound (or rather unsound) a chemical basis as Neoarsphenamin.

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